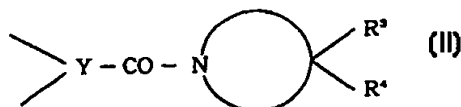
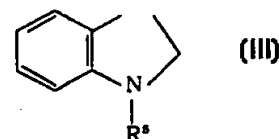
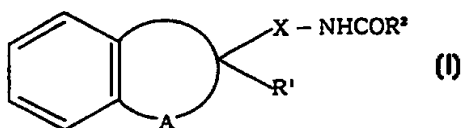




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(54) Title: PIPERIDINO DERIVATIVES WHICH PROMOTE GROWTH HORMONE RELEASE



## (57) Abstract

A pharmaceutically useful compound of formula (I) wherein R<sup>1</sup> is hydrogen and X is a group of formula (II) in which R<sup>3</sup> is esterified carboxy and R<sup>4</sup> is ar(lower) alkyl; R<sup>3</sup> is cyano and R<sup>4</sup> is aryl; R<sup>3</sup> is hydrogen and R<sup>4</sup> is 2-oxo-1-benzimidazolyl; or R<sup>3</sup> and R<sup>4</sup> are linked together to form formula (III) in which R<sup>5</sup> is acyl, formula (a) is piperidino, and Y is lower alkanetriyl; or R<sup>1</sup> is a group of formula (IV) in which R<sup>3</sup>, R<sup>4</sup> and formula (a) are each as defined above and X is bond, R<sup>2</sup> is 3-azetidiny, 4-piperidyl or a group of the formula: -Z-NHR<sup>6</sup> in which R<sup>6</sup> is hydrogen or amino protective group, and Z is lower alkylene or cyclo (lower) alkylene, and A is -(CH<sub>2</sub>)<sub>n</sub>-, in which n is 3, 4 or 5, or -CH=CH-(CH<sub>2</sub>)<sub>m</sub>-, in which m is 1, 2 or 3, and salts thereof. The compound or a salt thereof of the present invention has excellent promotion activity of growth hormone release for animals and human bodies.

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## DESCRIPTION

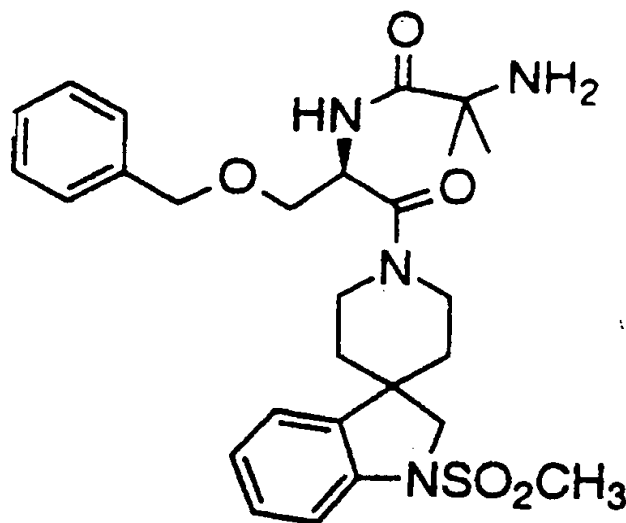
## PIPERIDINO DERIVATIVES WHICH PROMOTE GROWTH HORMONE RELEASE

## TECHNICAL FIELD

The present invention relates to novel derivatives and salts thereof.

## BACKGROUND ART

With regard to the states of the arts in this field, for example, the following compound is known.



WO94/13696

## DISCLOSURE OF INVENTION

The present invention relates to novel derivatives. More

particularly, it relates to novel derivatives and salts thereof which have pharmacological activities such as promotion activity of growth hormone release, to processes for preparation thereof, to pharmaceutical composition comprising the same, and to a use of the same as a medicament.

Accordingly, one object of the present invention is to provide the useful novel derivatives and salts thereof which have pharmacological activities such as a promotion activity of growth hormone release, and the like.

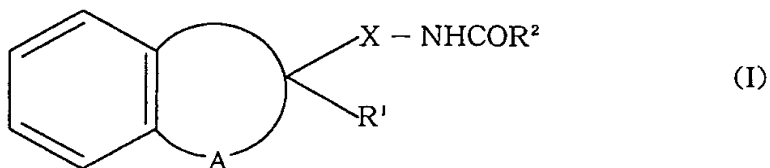
Another object of the present invention is to provide processes for the preparation of said novel derivatives and salts thereof.

A further object of the present invention is to provide a pharmaceutical composition comprising, as an active ingredient, said novel derivatives or a salt thereof.

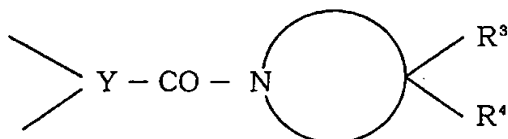
Still further object of this invention is to provide a use of said novel derivatives or a salt thereof as a medicament which promotes activity of growth hormone release for animals and human bodies and they are useful for treatment of obesity in combination with an  $\alpha 2$  or  $\beta 3$  adrenergic agonist, osteoporosis in combination with parathyroid hormone, the catabolic effects of nitrogen wasting in combination with insulin-like growth factor 1, growth retardation, renal failure or insufficiency, schizophrenia, sleep disorder, skeletal dysplasia, depression, Alzheimer's disease, pulmonary dysfunction, hyperinsulinemia, ulcer, arthritis, cardiac dysfunction, replacement for elderly people, ALS, growth hormone deficient adults, physiological short stature including growth hormone deficient children, Turner's syndrome, intrauterine growth retardation, cachexia and protein loss due to cancer or AIDS and is also useful for stimulating the immune system, accelerating wound healing or bone fracture repair, improvement in muscle

strength, and the like.

The object compounds of the present invention can be represented by the following general formula (I):



wherein R<sup>1</sup> is hydrogen and X is a group of the formula:



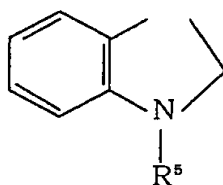
in which R<sup>3</sup> is esterified carboxy and

R<sup>4</sup> is ar(lower) alkyl;

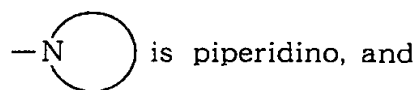
R<sup>3</sup> is cyano and R<sup>4</sup> is aryl;

R<sup>3</sup> is hydrogen and R<sup>4</sup> is 2-oxo-1-benzimidazoliny1; or

R<sup>3</sup> and R<sup>4</sup> are linked together to form

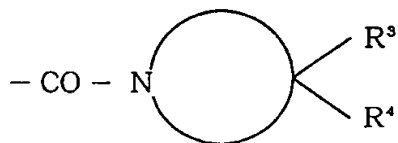



in which R<sup>5</sup> is acyl,



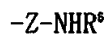
Y is lower alkanetriyl; or

R<sup>1</sup> is a group of the formula:



in which R<sup>3</sup>, R<sup>4</sup> and  are each as defined above and X is bond,

R<sup>2</sup> is 3-azetidiny, 4-piperidyl or a group of the formula:



in which R<sup>6</sup> is hydrogen or amino protective group, and

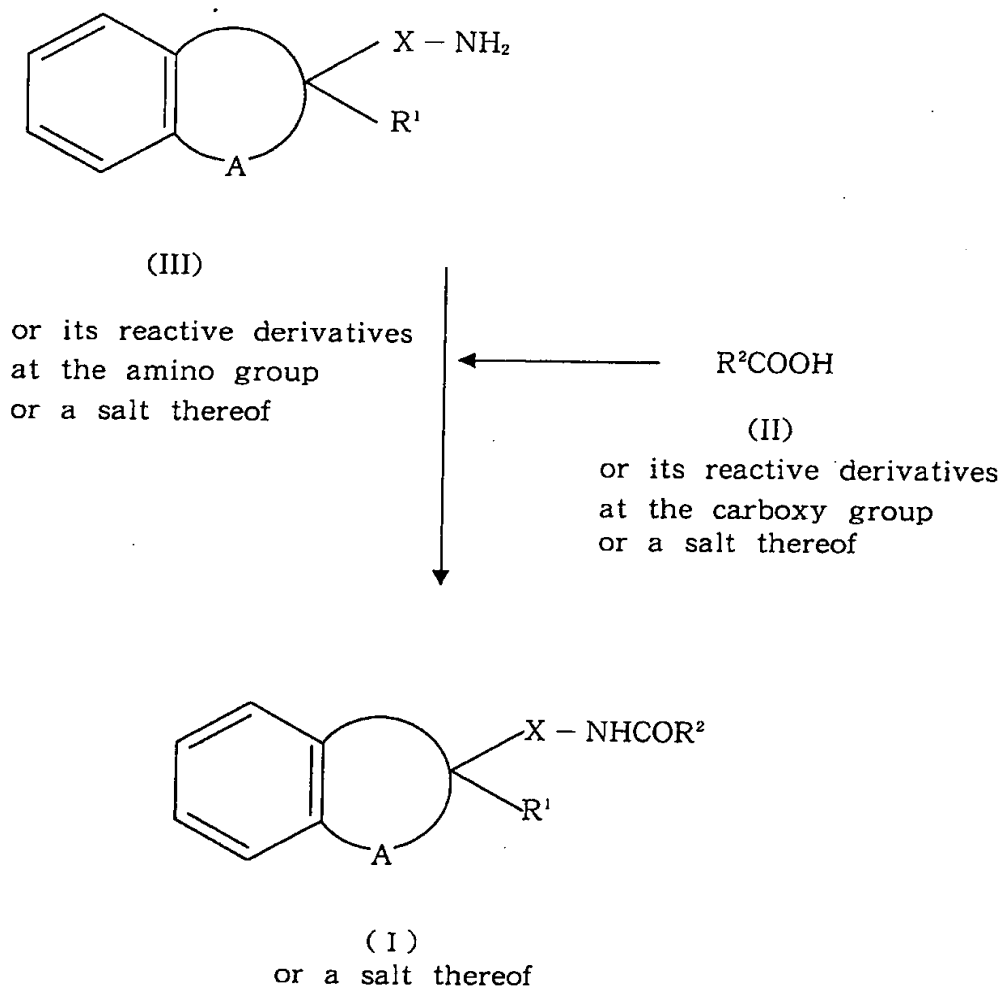
Z is lower alkylene or cyclo (lower) alkylene,

and

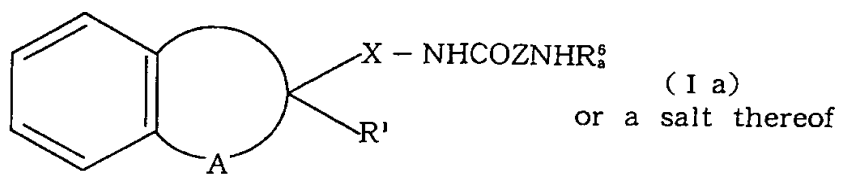
A is  $-(CH_2)_n-$ , in which n is 3, 4 or 5, or  
 $-CH=CH-(CH_2)_m-$ , in which m is 1, 2 or 3.

According to the present invention, the novel derivatives of the object compounds (I) can be prepared by the following processes.

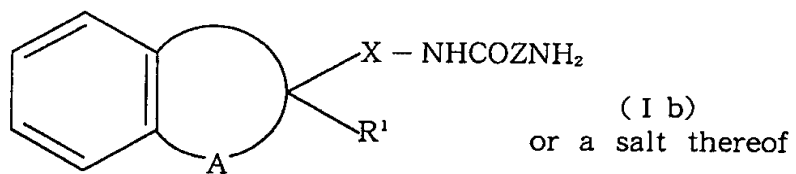
### Process 1



## Process 2

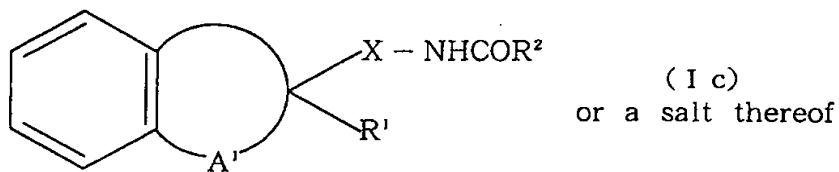


removal of amino  
protective group

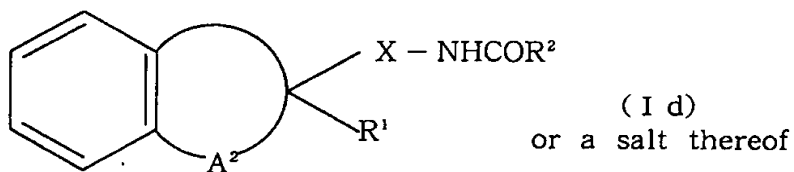




## Process 3



reduction



wherein  $R^1$ ,  $R^2$ , X, A and Z are each as  
defined above,

$R^6$  is amino protective group,

$A^1$  is  $-\text{CH}=\text{CH}-(\text{CH}_2)_m-$ , in which m is 1, 2 or 3, and

$A^2$  is  $-(\text{CH}_2)_n-$ , in which n is 3, 4 or 5.

Pharmaceutically acceptable salts of the object compounds (I)

are conventional non-toxic salts and may include an acid addition salt such as an inorganic acid addition salt [e.g. hydrochloride, hydrobromide, sulfate, phosphate, etc.], an organic acid addition salt [e.g. formate, acetate, trifluoroacetate, maleate, tartrate, methanesulfonate, benzenesulfonate, toluenesulfonate, etc.]; a salt with an amino acid [e.g. aspartic acid salt, glutamic acid salt, etc.]; and the like.

In the above and subsequent descriptions of the present specification, suitable examples and illustrations of the various definitions to be included within the scope of the invention are explained in detail as follows.

The term "lower" is intended to mean 1 to 6 carbon atom(s), preferably 1 to 4 carbon atom(s), unless otherwise indicated.

Suitable "lower alkylene" may include straight or branched one having 1 to 6 carbon atom(s), such as methylene, ethylene, propylene, trimethylene, tetramethylene, pentamethylene and dimethylmethylene.

"Amino protective group" may include acyl such as lower alkanoyl [e.g. formyl, acetyl, propionyl, pivaloyl, hexanoyl, etc.], mono(or di or tri)halo(lower)alkanoyl [e.g. chloroacetyl, bromoacetyl, dichloroacetyl, trifluoroacetyl, etc.], lower alkoxycarbonyl [e.g. methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl, t-butoxycarbonyl, t-pentyloxycarbonyl, hexyloxycarbonyl, etc.], carbamoyl, aroyl [e.g. benzoyl, toluoyl, naphthoyl, etc.], ar(lower)alkanoyl [e.g. phenylacetyl, phenylpropionyl, etc.], aryloxycarbonyl [e.g. phenoxy carbonyl, naphthylloxycarbonyl, etc.], aryloxy(lower)alkanoyl [e.g. phenoxyacetyl, phenoxypropionyl, etc.], arylglyoxyloyl [e.g. phenylglyoxyloyl, naphthylglyoxyloyl, etc.], ar(lower)alkoxycarbonyl

which may have suitable substituent(s) [e.g. benzyloxycarbonyl, phenethyloxycarbonyl, p-nitrobenzyloxycarbonyl, etc.]; ar(lower)alkyl such as ar(lower)alkylidene which may have substituent(s) [e.g. benzylidene, hydroxybenzylidene, etc.], mono(or di or tri)phenyl(lower)alkyl [e.g. benzyl, phenethyl, benzhydryl, trityl, etc.]; and the like.

Suitable "acyl" may include carbamoyl, aliphatic acyl and acyl group containing an aromatic ring, which is referred to as aromatic acyl, or an heterocyclic ring, which is referred to as heterocyclic acyl.

This acyl group may be derived, for example, from an organic carboxylic acid, an organic carbonic acid, an organic sulfuric acid, an organic sulfonic acid and an organic carbamic acid.

Suitable example of said acyl may be illustrated as follows:

Carbamoyl;

Aliphatic acyl such as lower or higher alkanoyl [e.g. formyl, acetyl, propanoyl, butanoyl, 2-methylpropanoyl, pentanoyl, 2,2-dimethylpropanoyl, hexanoyl, heptanoyl, octanoyl, nonanoyl, decanoyl, undecanoyl, dodecanoyl, tridecanoyl, tetradecanoyl, pentadecanoyl, hexadecanoyl, heptadecanoyl, octadecanoyl, nonadecanoyl, icosanoyl, etc.]; lower or higher cycloalkylcarbonyl [e.g. cyclopropylcarbonyl, cyclobutylcarbonyl, cyclopentylcarbonyl, cyclohexylcarbonyl, etc.]; lower or higher alkylsulfonyl [e.g. methylsulfonyl, ethylsulfonyl, etc.]; lower or higher alkoxysulfonyl [e.g. methoxysulfonyl, ethoxysulfonyl, etc.]; or the like;

Aromatic acyl such as aroyl [e.g. benzoyl, toluoyl, naphthoyl, etc.]; ar(lower)alkanoyl [e.g. phenyl(lower)alkanoyl (e.g. phenylacetyl, phenylpropanoyl, phenylbutanoyl, phenylisobutylyl, phenylpentanoyl, phenylhexanoyl, etc.), naphthyl(lower)alkanoyl (e.g. naphthylacetyl, naphthylpropanoyl, naphthylbutanoyl, etc.), etc.]; ar(lower)alkenoyl [e.

g. phenyl(lower)alkenoyl (e.g. phenylpropenoyl, phenylbutenoyl, phenylmethacryloyl, phenylpentenoyl, phenylhexenoyl, etc.), naphthyl(lower)alkenoyl (e.g. naphthylpropenoyl, naphthylbutenoyl, naphthylpentenoyl, etc.), etc.]; ar(lower)alkoxycarbonyl [e.g. phenyl(lower)alkoxycarbonyl (e.g. benzyloxycarbonyl, etc.), etc.]; aryloxycarbonyl [e.g. phenoxycarbonyl, naphthyloxycarbonyl, etc.]; aryloxy(lower)alkanoyl [e.g. phenoxyacetyl, phenoxypropionyl, etc.]; arylcarbamoyl [e.g. phenylcarbamoyl, etc.]; arylthiocarbamoyl [e.g. phenylthiocarbamoyl, etc.]; arylglyoxyloyl [e.g. phenylglyoxyloyl, naphthylglyoxyloyl, etc.]; arylsulfonyl [e.g. phenylsulfonyl, naphthylsulfonyl, etc.]; or the like;

Heterocyclic acyl such as heterocycliccarbonyl; heterocyclic(lower)alkanoyl [e.g. thienylacetyl, thienylpropanoyl, thienylbutanoyl, thienylpentanoyl, thienylhexanoyl, thiazolylacetyl, thiadiazolylacetyl, tetrazolylacetyl, etc.]; heterocyclic(lower)alkenoyl [e.g. heterocyclicpropenoyl, heterocyclicbutenoyl, heterocyclicpentenoyl, heterocyclichexenoyl, etc.]; heterocyclicglyoxyloyl [e.g. thiazolylglyoxyloyl, thienylglyoxyloyl, etc.]; or the like.

"Heterocyclic moiety" in the terms "heterocycliccarbonyl", "heterocyclic(lower)alkanoyl", "heterocyclic(lower)alkenoyl" and "heterocyclic glyoxyloyl" means saturated or unsaturated, monocyclic or polycyclic heterocyclic group containing at least one hetero-atom such as an oxygen, sulfur, nitrogen atom and the like.

Suitable "heterocyclic group" in the terms "heterocycliccarbonyl", "heterocyclic(lower)alkanoyl", "heterocyclic(lower)alkenoyl" and "heterocyclicglyoxyloyl" may include unsaturated 3 to 8-membered (more preferably 5 or 6-membered) heteromonocyclic group containing 1 to 4 nitrogen atom(s), for example, pyrrolyl, pyrrolinyl, imidazolyl, pyrazolyl, pyridyl and its N-oxide, dihydropyridyl,

pyrimidyl, pyrazinyl, pyridazinyl, triazolyl [e.g. 4H-1,2,4-triazolyl, 1H-1,2,3-triazolyl, 2H-1,2,3-triazolyl, etc.], tetrazolyl [e.g. 1H-tetrazolyl, 2H-tetrazolyl, etc.], etc.; saturated 3 to 8-membered (more preferably 5 or 6-membered) heteromonocyclic group containing 1 to 4 nitrogen atom(s), for example, pyrrolidinyl, imidazolidinyl, piperidino, piperazinyl, etc.; unsaturated condensed heterocyclic group containing 1 to 4 nitrogen atom(s), for example, indolyl, isoindolyl, indolinyl, indoliziny, benzimidazolyl, quinolyl, isoquinolyl, dihydroquinolyl, indazolyl, benzotriazolyl, etc.; unsaturated 3 to 8-membered (more preferably 5 or 6-membered) heteromonocyclic group containing 1 to 2 oxygen atom(s) and 1 to 3 nitrogen atom(s), for example, oxazolyl, isoxazolyl, oxadiazolyl [e.g. 1,2,4-oxadiazolyl, 1,3,4-oxadiazolyl, 1,2,5-oxadiazolyl, etc.], etc.; saturated 3 to 8-membered (more preferably 5 or 6-membered) heteromonocyclic group containing 1 to 2 oxygen atom(s) and 1 to 3 nitrogen atom(s), for example, morpholinyl, sydnonyl, etc.; unsaturated condensed heterocyclic group containing 1 to 2 oxygen atom(s) and 1 to 3 nitrogen atom(s), for example, benzoxazolyl, benzoxadiazolyl, etc.; unsaturated 3 to 8-membered (more preferably 5 or 6-membered) heteromonocyclic group containing 1 to 2 sulfur atom(s) and 1 to 3 nitrogen atom(s), for example, thiazolyl, isothiazolyl, thiadiazolyl [e.g. 1,2,3-thiadiazolyl, 1,2,4-thiadiazolyl, 1,3,4-thiadiazolyl, 1,2,5-thiadiazolyl, etc.], dihydrothiazinyl, etc.; saturated 3 to 8-membered (more preferably 5 or 6-membered) heteromonocyclic group containing 1 to 2 sulfur atom(s) and 1 to 3 nitrogen atom(s), for example, thiazolidinyl, etc.; unsaturated 3 to 8-membered (more preferably 5 or 6-membered) heteromonocyclic group containing 1 to 2 sulfur atom(s), for example, thienyl, dihydrodithiiny, dihydrodithionyl, etc.; unsaturated condensed heterocyclic group containing 1 to 2 sulfur atom(s) and 1 to 3 nitrogen

atom(s), for example, benzothiazolyl, benzothiadiazolyl, etc. ; unsaturated 3 to 8-membered (more preferably 5 or 6-membered) heteromonocyclic group containing an oxygen atom, for example, furyl, etc. ; unsaturated 3 to 8-membered (more preferably 5 or 6-membered) heteromonocyclic group containing an oxygen atom and 1 to 2 sulfur atom(s), for example, dihydrooxathiinyl, etc. ; unsaturated condensed heterocyclic group containing 1 to 2 sulfur atom(s), for example, benzothienyl [e.g. benzo [b]thienyl , etc. ], benzodithiinyl, etc. ; unsaturated condensed heterocyclic group containing an oxygen atom and 1 to 2 sulfur atom(s), for example, benzoxathiinyl, etc. and the like.

The acyl moiety as stated above may have 1 to 5, same or different, suitable substituent(s) such as halogen [e.g. fluorine, chlorine, bromine or iodine], lower alkyl [e.g. methyl, ethyl, propyl, isopropyl, butyl, isobutyl, t-butyl, pentyl, hexyl, etc.], lower alkoxy [e.g. methoxy, ethoxy, propoxy, isopropoxy, butoxy, t-butoxy, pentyloxy, hexyloxy, etc.], hydroxy, carboxy, protected hydroxy, protected carboxy, mono(or di or tri)halo(lower)alkyl, N,N-di(lower)alkylamino [e.g. N,N-dimethylamino, N,N-diethylamino, N,N-dipropylamino, N,N-dibutylamino, N,N-dipentylamino, N,N-dihexylamino, N-methyl-N-butylamino, etc.], or the like.

Suitable "lower alkanetriyl" may include methanetriyl, ethanetriyl and propanetriyl.

Suitable "cyclo(lower)alkylene" may include cyclopropylene, cyclobutylene, cyclopentylene and cyclohexylene.

Suitable "aryl" may include phenyl, naphthyl, tolyl, xylyl, mesityl, cumenyl, and the like, in which the preferable one is phenyl or naphthyl.

Suitable "ar(lower)alkyl" may include benzyl, phenethyl,

phenylpropyl, benzhydryl, trityl, and the like.

Suitable "ester moiety" in "esterified carboxy group" may include pharmaceutically acceptable, easily removable one such as lower alkyl ester (e.g. methyl ester, ethyl ester, propyl ester, isopropyl ester, butyl ester, isobutyl ester, t-butyl ester, pentyl ester, tert-pentyl ester, hexyl ester, etc.), lower alkenyl ester (e.g. vinyl ester, allyl ester, etc.), lower alkynyl ester (e.g. ethynyl ester, propynyl ester, etc.), lower alkoxy(lower)alkyl ester (e.g. methoxymethyl ester, ethoxymethyl ester, isopropoxymethyl ester, 1-methoxyethyl ester, 1-ethoxyethyl ester, etc.), lower alkylthio(lower)-alkyl ester (e.g. methylthiomethyl ester, ethylthiomethyl ester, ethylthioethyl ester, isopropylthiomethyl ester, etc.), carboxy-substituted-lower alkyl ester (e.g. carboxymethyl ester, 2-carboxyethyl ester, 3-carboxypropyl ester, etc.), protected carboxy-substituted-lower alkyl ester such as lower alkoxycarbonyl-substituted-lower alkyl ester (e.g. methoxycarbonylmethyl ester, tert-butoxycarbonylmethyl ester, 2-tert-butoxycarbonyl-ethyl ester, 3-tert-butoxycarbonylpropyl ester, etc.), protected carboxy-substituted-lower alkenyl ester such as lower alkoxycarbonyl-substituted-lower alkenyl ester (e.g. 2-isobutoxycarbonyl-2-pentenyl ester, etc.), mono(or di or tri)halo(lower)alkyl ester (e.g. 2-iodoethyl ester, 2,2,2-trichloroethyl ester, etc.), lower alkanoyloxy(lower)alkyl ester [e.g. acetoxymethyl ester, propionyloxymethyl ester, butyryloxymethyl ester, valeryloxymethyl ester, pivaloyloxymethyl ester, hexanoyloxymethyl ester, 1(or 2)-acetoxylethyl ester, 1(or 2 or 3)-acetoxypentyl ester, 1(or 2 or 3 or 4)-acetoxypentyl ester, 1(or 2)-propionyloxyethyl ester, 1(or 2 or 3)-propionyloxypropyl ester, 1(or 2)-butyryloxyethyl ester, 1(or 2)-isobutyryloxyethyl ester, 1(or 2)-pivaloyloxyethyl ester, 1(or 2)-hexanoyloxyethyl ester, isobutyryloxymethyl ester, 2-ethylbutyryloxymethyl ester, 3,3-dimethylbutyryloxymethyl ester, 1(or 2)

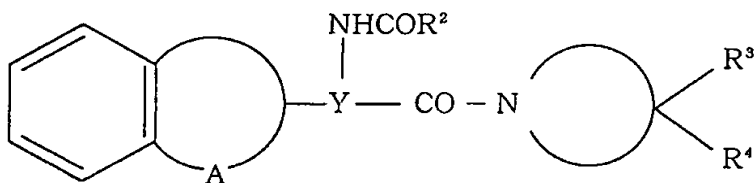
-pentanoyloxyethyl ester, etc. ], higher alkanoyloxy(lower)-alkyl ester [e.g. heptanoyloxymethyl ester, octanoyloxymethyl ester, nonanoyloxymethyl ester, decanoyloxymethyl ester, undecanoyloxymethyl ester, lauroyloxymethyl ester, tridecanoyloxymethyl ester, myristoyloxymethyl ester, pentadecanoyloxymethyl ester, palmitoyloxymethyl ester, heptadecanoyloxymethyl ester, stearoyloxymethyl ester, nonadecanoyloxymethyl ester, eicosanoyloxymethyl ester, 1(or 2)-heptanoyloxyethyl ester, 1(or 2)-octanoyloxyethyl ester, 1(or 2)-nonanoyloxyethyl ester, 1(or 2)-decanoyloxyethyl ester, 1(or 2)-undecanoyloxyethyl ester, 1(or 2)-lauroyloxyethyl ester, 1(or 2)-tridecanoyloxyethyl ester, 1(or 2)-myristoyloxyethyl ester, 1(or 2)-pentadecanoyloxyethyl ester, 1(or 2)-palmitoyloxyethyl ester, 1(or 2)-heptadecanyloxyethyl ester, 1(or 2)-stearoyloxyethyl ester, 1(or 2)-nonadecanoyl-oxyethyl ester, 1(or 2)-eicosanoyloxyethyl ester, etc. ], cycloalkylcarbonyloxy(lower)alkyl ester [e.g. cyclohexylcarbonyloxymethyl ester, 1(or 2) -cyclopentylcarbonyloxyethyl ester, 1 (or 2) -cyclohexylcarbonyloxyethyl ester, etc. ], aroyloxy (lower) alkyl ester such as benzoyloxy(lower) alkyl ester [e.g. 1 (or 2) -benzoyloxyethyl ester, etc. ], heterocycliccarbonyloxy(lower)alkyl ester such as lower alkylpiperidylcarbonyloxy(lower)alkyl ester [e.g. 1 (or 2) -(1-methylpiperidyl)carbonyloxyethyl, etc. ], lower alkoxycarbonyloxy(lower) alkyl ester [e.g. methoxycarbonyloxymethyl ester, ethoxycarbonyloxymethyl ester, propoxycarbonyloxymethyl ester, isopropoxycarbonyl-oxyethyl ester, tert-butoxycarbonyloxymethyl ester, 1(or 2)-methoxycarbonyloxyethyl ester, 1(or 2)-ethoxycarbonyloxyethyl ester, 1(or 2)-propoxycarbonyloxyethyl ester, 1(or 2)-isopropoxycarbonyloxyethyl ester, 1(or 2)-butoxycarbonyloxyethyl ester, 1(or 2)-isobutoxycarbonyloxyethyl ester, 1(or 2)-tert-



butoxycarbonyloxyethyl ester, 1(or 2)-hexyloxycarbonyloxy-ethyl ester, 1(or 2 or 3)-methoxycarbonyloxypropyl ester, 1(or 2 or 3)-ethoxycarbonyloxypropyl ester, 1(or 2 or 3)-isopropoxycarbonyloxypropyl ester, 1(or 2 or 3 or 4)-ethoxycarbonyloxybutyl ester, 1(or 2 or 3 or 4)-butoxycarbonyloxybutyl ester, 1(or 2 or 3 or 4 or 5)-pentyloxycarbonyloxypropyl ester, 1(or 2 or 3 or 4 or 5)-neopentyloxycarbonyloxypropyl ester, 1(or 2 or 3 or 4 or 5 or 6)-ethoxycarbonyloxyhexyl ester, etc.], cycloalkyloxycarbonyloxy(lower)alkyl ester [e.g. cyclohexyloxycarbonyloxymethyl ester, 1(or 2)-cyclopentyloxycarbonyloxyethyl ester, 1(or 2)-cyclohexyloxycarbonyloxyethyl ester, etc.], (5-lower alkyl-2-oxo-1,3-dioxol-4-yl)(lower)alkyl ester [e.g. (5-methyl-2-oxo-1,3-dioxol-4-yl)methyl ester, (5-ethyl-2-oxo-1,3-dioxol-4-yl)methyl ester, (5-propyl-2-oxo-1,3-dioxol-4-yl)ethyl ester, etc.], (5-lower alkyl-2-oxo-1,3-dioxolen-4-yl)(lower)alkyl ester [e.g. (5-methyl-2-oxo-1,3-dioxolen-4-yl)methyl ester, (5-tert-butyl-2-oxo-1,3-dioxolen-4-yl)methyl ester, etc.], (5-aryl-2-oxo-1,3-dioxolen-4-yl)(lower)alkyl ester such as (5-phenyl-2-oxo-1,3-dioxolen-4-yl)(lower)alkyl ester [e.g. (5-phenyl-2-oxo-1,3-dioxolen-4-yl)methyl ester, etc.], lower alkanesulfonyl(lower)alkyl ester (e.g. mesylmethyl ester, 2-mesylmethyl ester, etc.), ar(lower)alkyl ester which may have one or more substituent(s) such as mono-(or di or tri)phenyl(lower)alkyl ester which may have one or more suitable substituent(s) (e.g. benzyl ester, 4-methoxybenzyl ester, 4-nitrobenzyl ester, phenethyl ester, benzhydryl ester, trityl ester, bis(methoxyphenyl)-methyl ester, 3,4-dimethoxybenzyl ester, 4-hydroxy-3,5-di-t-butylbenzyl ester, etc.), aryl ester which may have one or more suitable substituents (e.g. phenyl ester, tolyl ester, t-butylphenyl ester, xylyl ester, mesityl ester, cumenyl ester, salicyl ester, etc.), heterocyclic ester (e.g. phthalidyl ester, 1(or 2)-phthalid-3-

ylideneethyl ester, etc.), and the like.

The preferred embodiments of the object compounds are shown in the following formula:

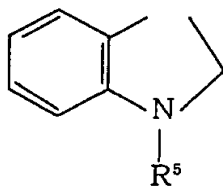


wherein  $R^3$  is lower alkoxy carbonyl and  $R^4$  is benzyl;

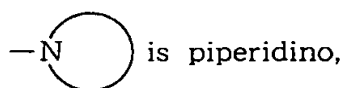
$R^3$  is cyano and  $R^4$  is phenyl;

$R^3$  is hydrogen and  $R^4$  is 2-oxo-1-benzimidazolinyll; or

$R^3$  and  $R^4$  are linked together to form

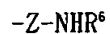


in which  $R^5$  is lower alkanesulfonyl,



Y is lower alkanetriyl,

R<sup>2</sup> is 3-azetidiny1, 4-piperidyl or a group of the formula:



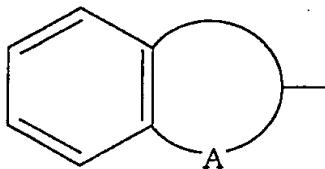
in which R<sup>6</sup> is hydrogen or lower alkoxy carbonyl, and

Z is lower alkylene or cyclo(lower) alkylene,

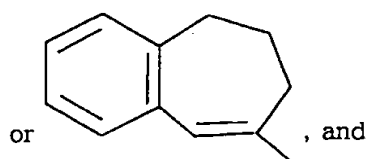
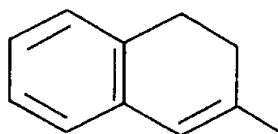
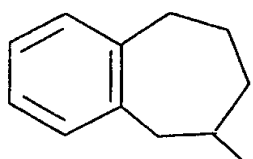
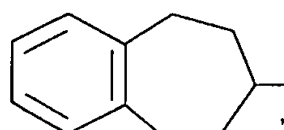
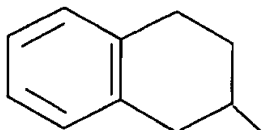
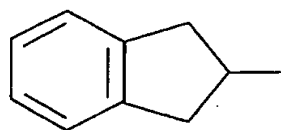
and A is  $-(CH_2)_n-$  in which n is 3, 4, or 5, or

$-CH=CH-(CH_2)_m-$ , in which m is 1, 2 or 3.

Further, the preferred embodiments of the following groups are as follows.

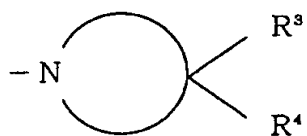


is the following formula :

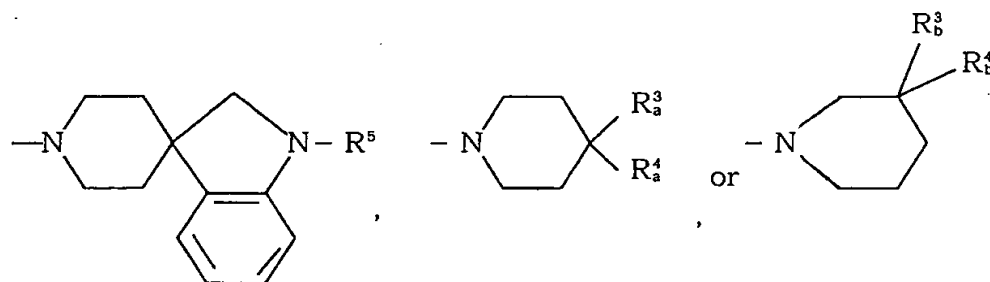


or

, and



is the following formula :



in which R<sup>5</sup> is lower alkanesulfonyl,

R<sub>a</sub><sup>3</sup> is hydrogen,

R<sub>a</sub><sup>4</sup> is 2-oxo-1-benzimidazoliny,

R<sub>b</sub><sup>3</sup> is lower alkoxy carbonyl and

R<sub>b</sub><sup>4</sup> is benzyl.

The processes for preparing the object compounds (I) are explained in detail in the following.

#### Process 1

The object compound (I) or a salt thereof can be prepared by reacting the compound (II) or its reactive derivatives at the carboxy group or a salt thereof with the compound (III) or its reactive derivatives at the amino group or a salt thereof.

Suitable reactive derivative at the carboxy group of the compound (II) may include an acid halide, an acid anhydride, an activated amide, an activated ester, and the like. Suitable examples of the reactive derivatives may be an acid chloride; an acid azide; a mixed acid anhydride within acid such as substituted phosphoric acid [e.

g. dialkylphosphoric acid, phenylphosphoric acid, diphenylphosphoric acid, dibenzylphosphoric acid, halogenated phosphoric acid, etc.], dialkylphosphorous acid, sulfurous acid, thiosulfuric acid, sulfuric acid, alkylcarbonic acid, (lower)alkanesulfonic acid [e.g. methanesulfonic acid, etc.], aliphatic carboxylic acid [e.g. acetic acid, propionic acid, butyric acid, isobutyric acid, pivalic acid, pentanoic acid, isopentanoic acid, 2-ethylbutyric acid, trichloroacetic acid, etc.] or aromatic carboxylic acid [e.g. benzoic acid, etc.]; a symmetrical acid anhydride; an activated amide with imidazole, 4-substituted imidazole, dimethylpyrazole, triazole or tetrazole; or an activated ester [e.g. cyanomethyl ester, methoxymethyl ester, dimethyliminomethyl  $[(\text{CH}_3)_2\text{N}^+=\text{CH}-]$  ester, vinyl ester, propargyl ester, p-nitrophenyl ester, 2,4-dinitrophenyl ester, trichlorophenyl ester, pentachlorophenyl ester, pentafluorophenyl ester, mesylphenyl ester, phenylazophenyl ester, phenyl thioester, p-nitrophenyl thioester, p-cresyl thioester, carboxymethyl thioester, pyranyl ester, pyridyl ester, piperidyl ester, 8-quinolyl thioester, etc.], or an ester with a N-hydroxy compound [e.g. N,N-dimethylhydroxylamine, 1-hydroxy-2-(1H)-pyridone, N-hydroxysuccinimide, N-hydroxyphthalimide, 1-hydroxy-1H-benzotriazole, etc.], and the like. These reactive derivatives can optionally be selected from them according to the kind of the compound (II) to be used.

Suitable salts of the compound (II) and its reactive derivative may be a base salt such as an alkali metal salt [e.g. sodium salt, potassium salt, etc.], an alkaline earth metal salt [e.g. calcium salt, magnesium salt, etc.], an ammonium salt, an organic base salt [e.g. trimethylamine salt, triethylamine salt, pyridine salt, picoline salt, dicyclohexylamine salt, N,N'-dibenzylethylenediamine salt, etc.], or the like, and an acid addition salt as exemplified for the compound (I).

The starting compound (III) or salts thereof are novel and can be prepared by the manners of Preparations mentioned below or a similar manner thereto.

Suitable reactive derivative at the amino group of the compound (III) may include Schiff's base type imino or its tautomeric enamine type isomer formed by the reaction of the compound (III) with a carbonyl compound such as aldehyde, ketone or the like; a silyl derivative formed by the reaction of the compound (III) with a silyl compound such as bis(trimethylsilyl)acetamide, mono(trimethylsilyl)acetamide, bis(trimethylsilyl)urea or the like; a derivative formed by reaction of the compound (III) with phosphorus trichloride or phosgene, and the like.

Suitable salts of the compound (III) and its reactive derivative can be referred to the ones as exemplified for the compound (I).

The reaction is usually carried out in a conventional solvent such as water, alcohol [e.g. methanol, ethanol, etc.], acetone, dioxane, acetonitrile, chloroform, methylene chloride, ethylene chloride, tetrahydrofuran, ethyl acetate, N,N-dimethylformamide, pyridine or any other organic solvent which does not adversely influence the reaction. These conventional solvent may also be used in a mixture with water.

In this reaction, when the compound (II) is used in a free acid form or its salt form, the reaction is preferably carried out in the presence of a conventional condensing agent such as carbodiimide or a salt thereof [e.g. N,N'-dicyclohexylcarbodiimide; N-cyclohexyl-N'-morpholinoethylcarbodiimide; N-cyclohexyl-N'-(4-di-ethylaminocyclohexyl)carbodiimide; N,N'-diethylcarbodiimide, N,N'-diisopropylcarbodiimide; N-ethyl-N'-(3-di-methylaminopropyl)carbodiimide or hydrochloride thereof], N,N'-carbonylbis-(2-methylimidazole); diphenyl phosphorylazide, diethyl phosphorocyanidate, bis (2-oxo-3-oxazolidinyl) phosphinic chloride, etc.; N,N'-carbonyldiimidazole, N,N'-carbonylbis-(2

-methylimidazole); keteneimine compounds [e.g. pentamethyleneketene-N-cyclohexylimine; diphenylketene-N-cyclohexylimine, etc.]; ethoxyacetylene; 1-alkoxy-1-chloroethylen; trialkyl phosphite; ethyl polyphosphate; isopropyl polyphosphate; phosphorus oxychloride (phosphoryl chloride); phosphorus trichloride; diphenyl phosphorylazide; thionyl chloride; oxalyl chloride; lower alkyl haloformate {e.g. ethyl chloroformate, isopropyl chloroformate, etc.}; triphenylphosphine; 2-ethyl-7-hydroxybenzisoxazolium salt; 2-ethyl-5-(m-sulfophenyl) isoxazolium hydroxide intramolecular salt; benzotriazol-1-yl-oxy-tris-(dimethylamino)phosphoniumhexafluorophosphate; 1-hydroxybenzotriazole, 1-(p-chlorobenzenesulfonyloxy)-6-chloro-1H-benzotriazole; so-called Vilsmeier reagent prepared by the reaction of N,N-dimethylformamide with thionyl chloride, phosgene, trichloromethyl chloroformate, phosphorus oxychloride, etc.; or the like.

The reaction may also be carried out in the presence of an inorganic or organic base such as an alkali metal bicarbonate, tri(lower)alkylamine, pyridine, N-(lower)alkylmorpholine, N,N-di(lower)alkylbenzylamine, or the like.

The reaction temperature is not critical, and the reaction is usually carried out under cooling, at ambient temperature or under warming.

## Process 2

The compound (Ib) or a salt thereof can be prepared by subjecting a compound (Ia) or a salt thereof to removal reaction of the amino-protective group in R<sup>a</sup>.

The starting compound (Ia) or a salts thereof are prepared by the process 1.

Suitable salts of the compounds (Ia) and (Ib) can be referred to



the ones as exemplified for the compound (I).

This reaction is carried out in accordance with a conventional manner such as hydrolysis, reduction or the like.

The hydrolysis is preferably carried out in the presence of a base or an acid including Lewis acid.

Suitable base may include an inorganic base and an organic base such as an alkali metal [e.g. sodium, potassium, etc.], an alkaline earth metal [e.g. magnesium, calcium, etc.], the hydroxide or carbonate or bicarbonate thereof, hydrazine, trialkylamine [e.g. trimethylamine, triethylamine, etc.], picoline, 1,5-diazabicyclo[4.3.0]-non-5-ene, 1,4-diazabicyclo[2.2.2]octane, 1,8-diazabicyclo[5.4.0]undec-7-ene, or the like.

Suitable acid may include an organic acid [e.g. formic acid, acetic acid, propionic acid, trichloroacetic acid, trifluoroacetic acid, etc.], an inorganic acid [e.g. hydrochloric acid, hydrobromic acid, sulfuric acid, hydrogen chloride, hydrogen bromide, hydrogen fluoride, etc.] and an acid addition salt compound [e.g. pyridine hydrochloride, etc.].

The elimination using Lewis acid such as trihaloacetic acid [e.g. trichloroacetic acid, trifluoroacetic acid, etc.] or the like is preferably carried out in the presence of cation trapping agents [e.g. anisole, phenol, etc.].

The reaction is usually carried out in a solvent such as water, an alcohol [e.g. methanol, ethanol, etc.], methylene chloride, diethyl ether, dioxane, chloroform, tetrachloromethane, tetrahydrofuran, ethyl acetate, a mixture thereof or any other solvent which does not adversely influence the reaction. A liquid base or acid can be also used as the solvent.

The reaction temperature is not critical and the reaction is

usually carried out under cooling, at ambient temperature or under heating.

The reduction method applicable for the elimination reaction may include chemical reduction and catalytic reduction.

Suitable reducing agents to be used in chemical reduction are a combination of metal [e.g. tin, zinc, iron, etc.] or metallic compound [e.g. chromium chloride, chromium acetate, etc.] and an organic or inorganic acid [e.g. formic acid, acetic acid, propionic acid, trifluoroacetic acid, p-toluenesulfonic acid, hydrochloric acid, hydrobromic acid, etc.].

Suitable catalysts to be used in catalytic reduction are conventional ones such as platinum catalysts [e.g. platinum plate, spongy platinum, platinum black, colloidal platinum, platinum oxide, platinum wire, etc.], palladium catalysts [e.g. spongy palladium, palladium black, palladium oxide, palladium on carbon, colloidal palladium, palladium on barium sulfate, palladium on barium carbonate, etc.], nickel catalysts [e.g. reduced nickel, nickel oxide, Raney nickel, etc.], cobalt catalysts [e.g. reduced cobalt, Raney cobalt, etc.], iron catalysts [e.g. reduced iron, Raney iron etc.], copper catalysts [e.g. reduced copper, Raney copper, Ullman copper, etc.] and the like.

The reduction is usually carried out in a conventional solvent which does not adversely influence the reaction such as water, methanol, ethanol, propanol, N,N-dimethylformamide, acetone, or a mixture thereof.

Additionally, in case that the above-mentioned acid to be used in chemical reduction are in liquid, they can also be used as a solvent. Further, a suitable solvent to be used in catalytic reduction may be the above-mentioned solvent, and other conventional solvent such as diethyl ether, dioxane, tetrahydrofuran, etc., or a mixture thereof.

The reaction temperature of this reduction is not critical and the reaction is usually carried out under cooling, at ambient temperature or under heating.

### Process 3

The object compound (Id) or a salt thereof can be prepared by subjecting the compound (Ic) or a salt thereof to the reduction reaction.

Reduction is carried out in a conventional manner, including chemical reduction and catalytic reduction.

Suitable reducing agents to be used in chemical reduction are a combination of metal [e. g. tin, zinc, iron, etc.] or metallic compound [e. g. chromium chloride, chromium acetate, etc.] and an organic or inorganic acid [e. g. formic acid, acetic acid, propionic acid, trifluoroacetic acid, p-toluenesulfonic acid, hydrochloric acid, hydrobromic acid, etc.].

Suitable catalysts to be used in catalytic reduction are conventional ones such as platinum catalysts [e. g. platinum plate, spongy platinum, platinum black, colloidal platinum, platinum oxide, platinum wire, etc.], palladium catalysts [e. g. spongy palladium, palladium black, palladium oxide, palladium on carbon, colloidal palladium, palladium on barium sulfate, palladium on barium carbonate, etc.], nickel catalysts [e. g. reduced nickel, nickel oxide, Raney nickel, etc.], cobalt catalysts [e. g. reduced cobalt, Raney cobalt, etc.], iron catalysts [e. g. reduced iron, Raney iron etc.], copper catalysts [e. g. reduced copper, Raney copper, Ullman copper, etc.] and the like.

The reduction is usually carried out in a conventional solvent which does not adversely influence the reaction such as

water, methanol, ethanol, propanol, N, N-dimethylformamide, or a mixture thereof. Additionally, in case that the above-mentioned acid to be used in chemical reduction are in liquid, they can also be used as a solvent. Further, a suitable solvent to be used in catalytic reduction may be the above-mentioned solvent, and other conventional solvent such as diethyl ether, dioxane, tetrahydrofuran, etc., or a mixture thereof.

The reaction temperature of this reduction is not critical and the reaction is usually carried out under cooling to warming.

The compounds obtained by the above processes can be isolated and purified by a conventional manner such as pulverization, recrystallization, column chromatography, reprecipitation, or the like.

The object compounds (I) thus obtained can be converted to its salt by a conventional manner.

The object compounds (I) and salt thereof may include a solvate [e.g., enclosure compound (e.g., hydrate, etc.)].

The object compounds (I) and salts thereof are expected to possess excellent pharmacological activities such as promotion activity of growth hormone release for animals and human bodies and they are useful for treatment of obesity in combination with an  $\alpha 2$  or  $\beta 3$  adrenergic agonist, osteoporosis in combination with parathyroid hormone, the catabolic effects of nitrogen wasting in combination with insulin-like growth factor 1, growth retardation, renal failure or insufficiency, schizophrenia, sleep disorder, skeletal dysplasia, depression, Alzheimer's disease, pulmonary dysfunction, hyperinsulinemia, ulcer, arthritis, cardiac dysfunction, replacement for elderly people, ALS, growth hormone deficient adults, physiological short

stature including growth hormone deficient children, Turner's syndrome, intrauterine growth retardation, cachexia and protein loss due to cancer or AIDS and is also useful for stimulating the immune system, accelerating wound healing or bone fracture repair, improvement in muscle strength, and the like.

In order to illustrate the usefulness of the object compounds (I), the pharmacological test data of the representative compound of the compounds (I) are shown in the following.

Test: Promotion activity of growth hormone release

(1) Test Method

Male wistar rats (6 week) were anaesthetized with ether. 0.6ml Blood samples were collected before and 5 min. after compounds injection. The secretagogues were given i.v. All compounds were dissolved in saline. Rat GH was measured by RIA (radioimmunoassay) in serum.

(2) Test compound

(a) 2-Amino-N-[[1-(1,2-benzocyclohepten-5-yl)-2-oxo-2-(1-methanesulfonylspiro[indoline-3,4'-piperidine]-1'-yl)]ethyl]-2-methylpropanamide hydrochloride.

(3) Test Result

Test Compound	Increasing ratio(%) of G. H. release
	1 mg/kg dosage
(a)	2944

G. H. = Growth Hormone

For therapeutic or preventive administration, the object compounds (I) of the present invention and pharmaceutically acceptable salts thereof are used in the form of the conventional pharmaceutical preparation which contains said compounds as an active ingredient, in admixture with a conventional pharmaceutically acceptable carrier such as an organic or inorganic solid or liquid excipient suitable for oral, parenteral or external administration. If needed, there may be included in the above preparation auxiliary substance such as stabilizing agent, wetting or emulsifying agent, buffer or any other commonly used additives.

The effective ingredient may usually be administered with a unit dose of 0.001 mg/kg to 100 mg/kg/day, preferably 0.01 mg/kg to 50 mg/kg, 1 to 4 times a day. However, the above dosage may be increased or decreased according to age, weight and conditions of the patient or the administering method.

The following Preparations and Examples are given for the purpose of illustrating the present invention in more detail.

#### Preparation 1

To a suspension of sodium hydride(15.12g, 60% oil) in

tetrahydrofuran(1.5l) was added carefully diethyl malonate(30.3g) at 0°C under nitrogen atmosphere. After stirred for 30 minutes, to the reaction mixture was added by portions 0-xylene dibromide(50g), and which was stirred for additional 24 hours at ambient temperature.

To the reaction mixture was added glacial acetic acid at 0°C and insoluble material was removed by filtration and the mother liquor was concentrated in vacuo, which was added ethyl acetate and poured into water. Organic layer was separated.

Aqueous layer was reextracted with ethyl acetate. Organic layers were combined, washed in turn with water, saturated sodium chloride in water and dried over magnesium sulfate.

Evaporation of the solvent gave a residue, which was chromatographed on silica-gel eluting with 20% ethyl acetate in n-hexane to give 2,2-diethoxycarbonylindan(43.64g).

IR(neat); 2983, 1734, 1456, 1369, 1282, 1248, 1186, 1163cm<sup>-1</sup>

<sup>1</sup>H NMR(DMSO-d<sup>6</sup>)  $\delta$ : 1.17(6H, t, J=7.1Hz), 3.48(4H, s), 4.14(4H, q, J=7.1Hz), 7.13 - 7.25(4H, m),

(+)APCI MS m/z; 263(M<sup>+</sup>+1).

## Preparation 2

To a solution of 2,2-diethoxycarbonylindan(30g) in dimethyl sulfoxide(300ml) was added a solution of lithium chloride(12.1g) in water (30ml), which was refluxed for 18 hours at 210°C.

The reaction mixture was extracted with 50% ethyl acetate in n-hexane. Organic layer was washed in turn with water, saturated sodium chloride in water and dried over magnesium sulfate. Evaporation of the solvent gave a residue, which was chromatographed on silica-gel eluting with 9% ethyl acetate in n-hexane to give 2-ethoxycarbonylindan(14.07g).

IR(neat); 2979, 1734, 1471, 1454, 1375, 1257, 1211, 1169cm<sup>-1</sup>

$^1\text{H}$  NMR( $\text{CDCl}_3$ )  $\delta$ : 1.28(3H, t,  $J=7.2\text{Hz}$ ), 3.15-3.40(5H, m), 4.12-4.26(2H, m), 7.12 - 7.14(4H, m),  
(+)APCI MS  $m/z$ ; 191( $M^+1$ ).

### Preparation 3

To a suspension of lithium aluminum hydride(3.1g) in tetrahydrofuran(160ml) was added carefully 2-ethoxycarbonylindan(7.79g) at  $0^\circ\text{C}$  under nitrogen atmosphere. After stirred for 2 hours at ambient temperature, the reaction mixture was added in turn with water(7.8ml), 4N-aqueous sodium hydroxide solution(7.8ml), water(23.4ml) and magnesium sulfate.

Insoluble material was removed by filtration and the mother liquor was concentrated in vacuo to give 2-hydroxymethylindan(5.8g).

IR(neat); 3338, 2933, 1471,  $1034\text{cm}^{-1}$ .

$^1\text{H}$  NMR( $\text{CDCl}_3$ )  $\delta$ : 2.60-2.85(3H, m), 3.00-3.15(2H, m), 3.67(2H, d,  $J=6.4\text{Hz}$ ), 7.10-7.26(4H, m)

(+)APCI MS  $m/z$  ; 149( $M^+1$ ).

### Preparation 4

To a solution of 2-hydroxymethylindan in ethyl acetate(100ml) was added in turn with triethylamine(5.58ml) and methanesulfonylchloride (2.95ml) at  $0^\circ\text{C}$  under nitrogen atmosphere. After stirred for 18 hours at ambient temperature, insoluble material was removed by filtration and the mother liquor was poured into 1N aqueous hydrochloric acid. Organic layer was separated, which was washed in turn with saturated sodium chloride in water, saturated sodium hydrogen carbonate in water, brine and dried over magnesium sulfate.

Evaporation of the solvent gave 2-methanesulfonyloxymethylindan (7.81g).



IR(KBr); 1471, 1414, 1344, 1173, 947 $\text{cm}^{-1}$

$^1\text{H}$  NMR( $\text{CDCl}_3$ )  $\delta$ : 2.70-3.20(8H, m), 4.23(2H, d,  $J$ =(6.7Hz), 7.10 - 7.26 (4H, m)

(+)APCI MS  $m/z$ ; 227( $M^+$ +1).

#### Preparation 5

To a solution of 2-methansulfonyloxymethylindan(7g) in N,N-dimethylformamide(50ml) was added sodium iodide (7.7g), which was stirred at 85°C for 3 hours. The reaction mixture was extracted with 50 % ethyl acetate in n-hexane. Organic layer was washed in turn with water, brine and dried over magnesium sulfate. Evaporation of the solvent gave a residue, which was chromatographed on silica-gel eluting n-hexane to give 2-iodomethylindan (5.59g).

IR(neat); 2939, 1595, 1473, 1433, 1217, 1176  $\text{cm}^{-1}$ .

$^1\text{H}$  NMR( $\text{CDCl}_3$ )  $\delta$ : 2.65-2.90(3H, m), 3.00-3.20(2H, m), 3.34(2H, d,  $J$ =6.7Hz), 7.10-7.25(4H, m)

(+)FAB/MS  $m/z$  ; 259( $M^+$ +1).

#### Preparation 6

To ethanol(34ml) was added carefully sodium(1.5g) at ambient temperature, and stirred for 30 minutes at 40°C. To the solution was added acetylaminomalonic acid diethyl ester(14.1g) and 2-iodomethylindan (5.59g) in tetrahydrofuran(30ml), and which was refluxed for 18 hours. Evaporation of the solvent gave a residue, which was added ethyl acetate and poured into water.

Organic layer was separated. Aqueous layer was reextracted with ethyl acetate. Organic layers were combined, and washed in turn with water, brine and dried over magnesium sulfate. Evaporation of the solvent gave a residue, which was chromatographed on silica-gel eluting

in turn with 50% ethyl acetate in n-hexane and ethyl acetate to give ethyl 2-acetamido-2-ethoxycarbonyl-3-(indan-2-yl) propionate(8.1g).

IR(KBr); 3253, 2985, 1745, 1643, 1525, 1439, 1379, 1230, 1215, 1176  $\text{cm}^{-1}$ .

$^1\text{H}$  NMR( $\text{CDCl}_3$ )  $\delta$ : 1.23-1.34(6H, m), 2.06(3H, s), 2.20-2.45(1H, m), 2.50-2.75(4H, m), 2.89-3.01(2H, m), 4.19-4.35(4H, m), 6.89(1H, s), 7.05-7.20(4H, m)  
(+)APCI MS  $m/z$ ; 348( $M^+1$ ).

#### Preparation 7

To a solution of ethyl 2-acetamido-2-ethoxycarbonyl-3-(indan-2-yl) propionate(8g) in ethanol(40ml) was added a solution of potassium hydroxide(2.58g) in water(40ml), and which was refluxed for 3 hours. Evaporation of the solvent gave a residue, which was added water(100ml) and washed with ethyl acetate. Aqueous layer was acidified with 2N-aqueous hydrochloric acid and extracted with ethyl acetate. Organic layer was separated and washed in turn with water, brine and dried over magnesium sulfate.

Evaporation of the solvent gave 2-acetamido-3-(indan-2-yl) propionic acid (3.27g). IR(KBr); 3342, 2937, 2629, 2511, 1709, 1618, 1543, 1275  $\text{cm}^{-1}$ .

$^1\text{H}$  NMR( $\text{CD}_3\text{OD}$ )  $\delta$ : 1.80-2.09(5H, m), 2.40-2.70(3H, m), 2.95-3.10(2H, m), 4.48(1H, dd,  $J=5.2, 9.5\text{Hz}$ ), 7.04-7.18(4H, m)

#### Preparation 8

A suspension of 2-acetamido-3-(indan-2-yl)propionic acid(3.27g) in 1N-aqueous hydrochloric acid(50ml) was stirred at ambient temperature for 18 hours. Evaporation of the solvent gave a residue, which was washed with diethyl ether to give 2-amino-3-(indan-2-yl) propionic acid hydrochloride(3.16g).

IR(KBr); 2985, 1809, 1765, 1579, 1487, 1373, 1309, 1261, 1213 $\text{cm}^{-1}$ .

$^1\text{H}$  NMR( $\text{D}_2\text{O}$ )  $\delta$ : 1.99-2.28(2H, m), 2.55-2.71(2H, m), 3.10-3.25(2H, m), 4.12(1H, t,  $J=6.9\text{Hz}$ ), 7.19-7.33(4H, m)

(+)APCI MS  $m/z$ ; 206( $M^++1$ ).

#### Preparation 9

To a solution of 2-amino-3-(indan-2-yl)propionic acid hydrochloride(3.1g) in a mixture of water(30ml) and 1,4-dioxane(30ml) was added di-tert-butylidicarbonate(2.47g) and triethylamine(4.1ml), and which was stirred for 18 hours at ambient temperature. Evaporation of the solvent gave a residue, which was acidified to pH 2 with 1N-aqueous hydrochloric acid, and extracted twice with ethyl acetate. The extracts were combined, dried over magnesium sulfate, and evaporated in vacuo to give 2-t-butoxycarbonylamino-3-(indan-2-yl)propionic acid(3.76g).

IR(KBr); 3376, 3323, 1749, 1664, 1539, 1450, 1400, 1296 $\text{cm}^{-1}$ .

$^1\text{H}$  NMR( $\text{DMSO}-d_6$ )  $\delta$ : 1.38(9H, s), 1.70-1.90(2H, m), 2.40-2.65(1H, m), 2.80-3.10(2H, m), 3.90-4.10(1H, m), 7.05-7.25(4H, m), 12.48(1H, br, s).

#### Preparation 10

1-Ethyl-3-(3'-dimethylaminopropyl)carbodiimide(0.84ml) was added to a mixture of 2-t-butoxycarbonylamino-3-(indan-2-yl) propionic acid (1g), 1-methanesulfonylspiro[indoline-3,4'-piperidine] hydrochloride(1.07g) and 1-hydroxybenzotriazole(574mg) in dichloromethane(20ml) at ambient temperature and the resulting mixture was stirred at the same temperature overnight.

The reaction mixture was partitioned between ethyl acetate and water. The organic layer was separated, washed with water, brine, and dried over magnesium sulfate, and evaporated in vacuo to give 1'-[2-tert-butoxycarbonylamino-3-(indan-2-yl)propionyl]-1-methanesulfonylspiro

[indoline-3,4'-piperidine](1.91g).

IR(KBr); 2931, 1709, 1643, 1516, 1456, 1350, 1252, 1163 $\text{cm}^{-1}$ .

$^1\text{H}$  NMR( $\text{CDCl}_3$ )  $\delta$ : 1.46(9H, s), 1.80-1.95(6H, m), 2.50-3.40(10H, m), 3.85-4.15(3H, m), 4.50-4.90(2H, m), 5.42(1H, d,  $J=8.8\text{Hz}$ ), 7.04-7.42(8H, m).

(+)APCI MS  $m/z$ ; 454( $\text{M}^+-\text{CO}_2\text{Bu}+2$ ), 498( $\text{M}^+-\text{C}(\text{CH}_3)_3+1$ ).

#### Preparation 11

Trifluoroacetic acid(4ml) was added to a solution of 1'-[2-tert-butoxycarbonylamino-3-(indan-2-yl)propionyl]-1-methanesulfonylspiro[indoline-3,4'-piperidine](1.81g) in dichloromethane(40ml) at ambient temperature and the resulting mixture was stirred at the same temperature overnight.

The reaction mixture was evaporated in vacuo and partitioned between ethyl acetate and saturated sodium hydrogen carbonate in water.

The organic layer was separated, washed with water and brine, dried over magnesium sulfate, and evaporated in vacuo to give 1'-[2-amino-3-(indan-2-yl)propionyl]-1-methanesulfonylspiro[indoline-3,4'-piperidine](1.41g).

IR(KBr); 2935, 1732, 1691, 1637, 1479, 1346, 1161 $\text{cm}^{-1}$ .

$^1\text{H}$  NMR( $\text{CDCl}_3$ )  $\delta$ : 1.70-2.00(6H, m), 2.50-2.90(6H, m), 2.92(3H, s), 2.95-3.35(3H, m), 3.79-4.05(4H, m), 4.50-4.80(1H, m), 7.03-7.42(8H, m),

(+)APCI MS  $m/z$ ; 454( $\text{M}^++1$ ).

#### Preparation 12

To a suspension of potassium t-butoxide (840mg) in tetrahydrofuran (20ml) was added (methoxymethyl)triphenylphosphonium chloride (2.1g). After being stirred for 15 minutes at room temperature, to the reaction mixture was added 4,5-benzocycloheptenone (1g) and the resulting mixture was stirred for additional 4 hours at the same temperature. The

solvent was evaporated in vacuo and the residue was partitioned between ethyl acetate and water. The organic layer was washed with water (twice) and brine, dried over magnesium sulfate, and evaporated in vacuo to give the residue. To a solution of residue in diethyl ether (10ml), was added dropwise perchloric acid (1ml) at 0 °C and the resulting mixture was stirred at the same temperature for 3 hours. The reaction mixture was partitioned between diethyl ether and water. The organic layer was separated, washed with water (three times) and brine, dried over magnesium sulfate, and evaporated in vacuo, to afford 5-formyl-1,2-benzocycloheptene(900mg) as an oil.

$^1\text{H NMR}(\text{CDCl}_3) \delta$  : 1.53-1.66(4H, m), 2.12-2.24(1H, m), 2.53-2.92(4H, m), 7.11-7.22(4H, m), 9.67(1H, s)

#### Preparation 13

A stirred suspension of 5-formyl-1,2-benzocycloheptene(900mg), sodium cyanide (758mg), and ammonium carbonate (4.8g) in a mixture of methanol (20ml) and water (20ml) was refluxed for 18 hours. The methanol was evaporated in vacuo, and the remaining was allowed to stand at 0°C and stirred for 3 hours. The insoluble material was collected by filtration, washed with water and dried to give 5-(1,2-benzocyclohepten-5-yl)hydantoin (730mg) as a solid.

FT IR(KBr) : 3315, 3238, 1726, 1714, 1452, 1415  $\text{cm}^{-1}$

$^1\text{H NMR}(\text{DMSO}-d_6) \delta$  : 1.16-1.27(2H, m), 1.62-2.08(3H, m), 2.52-2.77(4H, m), 3.97(1H, d, J=2.0Hz), 7.04-7.10(4H, m), 7.84(1H, s), 10.57(1H, br. s)

(+)APCI MS m/z : 245( $\text{M}^+$  +1)

#### Preparation 14

5-(1,2-benzocyclohepten-5-yl)hydantoin (500mg) was hydrolyzed with a suspension of calcium hydroxide (1.8g) in water (20ml) at 130°C in a

sealed tube for 6 hours.

The insoluble material was removed by filtration. To the filtrate was added di-tert-butylidicarbonate (429mg), triethylamine (2ml), and 1,4-dioxane (30ml), and the mixture was stirred for 18 hours at ambient temperature. Evaporation of the solvent gave a residue, which was acidified to pH 2 with 1N-hydrochloric acid and extracted twice with ethyl acetate. The extracts were combined, dried over magnesium sulfate, and evaporated in vacuo to give 2-t-butoxycarbonylamino-2-(1,2-benzocyclohepten-5-yl)acetic acid (380mg) as an oil.

$^1\text{H NMR}(\text{CDCl}_3) \delta$  : 1.26-1.42(2H, m), 1.45(9H, s), 1.90-2.04(3H, m), 2.80-2.82(4H, m), 4.07-4.18(1H, m), 4.94-4.96(1H, m), 7.11-7.23(4H, m)

#### Preparation 15

1-Ethyl-3-(3'-dimethylaminopropyl)carbodiimide (0.3ml) was added to a mixture of 2-t-butoxycarbonylamino-2-(1,2-benzocyclohepten-5-yl)acetic acid (380mg), 1-methanesulfonylspiro[indoline-3,4'-piperidine]hydrochloride (387.6mg) and 1-hydroxybenzotriazole (207.6mg) in dichloromethane (20ml) at an ambient temperature and the resulting mixture was stirred at the same temperature overnight.

The reaction mixture was partitioned between ethyl acetate and water. The organic layer was separated, washed with water and brine, dried over magnesium sulfate, and evaporated in vacuo to give a residue.

Trifluoro acetic acid (1ml) was added to a solution of the residue in dichloromethane (10ml) at ambient temperature and the mixture was stirred for 4 hours. The reaction mixture was evaporated in vacuo and partitioned between ethyl acetate and a saturated solution of sodium hydrogen carbonate in water. The organic layer was separated, washed with water and brine, dried over magnesium sulfate, and evaporated in vacuo to give 1'-[2-amino-2-(1,2-benzocyclohepten-5-yl)acetyl]-1-

methanesulfonylspiro[indoline-3,4'-piperidine] (450mg) as a powder.

$^1\text{H NMR}(\text{CDCl}_3) \delta$  : 1.60-1.81(10H, m), 2.05(3H, s), 2.80-2.90(5H, m), 2.93(2H, s), 3.60-3.70(1H, m), 4.08-4.12(2H, m), 7.1-7.39(8H, m)

#### Preparation 16

2-tert-Butoxycarbonylaminoindan-2-carboxylic acid was prepared according to a similar manner to that of Preparation 9.

FT IR(film) : 3394, 1755, 1660, 1518, 1381, 1369, 1296, 1232, 1159, 1122 $\text{cm}^{-1}$

$^1\text{H NMR}(\text{CDCl}_3) \delta$  : 1.43(9H, s), 3.24(2H, d, J=16.5Hz), 3.71(2H, d, J=16.5Hz), 5.15(1H, br. s), 7.13-7.21(4H, m)

#### Preparation 17

(2-Amino-indan-2-yl)-1-methanesulfonylspiro[indoline-3,4'-piperidine-1'-yl]methanone was prepared according to similar manners to those of Preparation 10, and successively Preparation 11.

(+)APCI MS  $m/z$  : 426( $M^+ + 1$ )

#### Preparation 18

2-Acetamide-3-(indan-2-yl)propionic acid (2.3g) was dissolved in a mixture of 1N aqueous sodium hydroxide solution (10.23ml) and water (23ml), and the resulting solution was adjusted to pH 8.0 with 1N hydrochloric acid. Then the resulting mixture was allowed to warm to 37 °C, and therein was added cobalt (II) chloride hexahydrate (11.5mg) and acylase (acylase amano (11.5mg).

After adjusting to pH 7.5, the reaction mixture was stirred for 24 hours while keeping the temperature at 37°C. To the resulting mixture was added water until insoluble material disappeared, and the pH was adjusted to pH 1.9 with conc- hydrochloric acid. The mixture was

partitioned between ethyl acetate and water. The organic layer was separated and the aqueous layer was reextracted with ethyl acetate. The organic layers were combined respectively.

The organic layer was washed with 1N hydrochloric acid, water, and brine, and dried over magnesium sulfate. Evaporation of the solvent gave crude (2R)-2-acetamide-3-(indan-2-yl)propionic acid as an optically impure foam (1.07g).

The aqueous layer was washed with ethyl acetate, concentrated in vacuo, and azeotroped twice with toluene. The residue was collected, washed with toluene, and dried under a reduced pressure to give (2S)-2-amino-3-(indan-2-yl)propionic acid hydrochloride as a solid (830mg)

$^1\text{H NMR}(\text{D}_2\text{O}) \delta$  : 2.00-2.15(2H, m), 2.55-2.80(3H, m), 3.10-3.25(2H, m), 3.70-3.90(1H, m), 7.20-7.35(4H, m).

(+)APCI MS  $m/z$  : 206( $M^+ + 1$ )

#### Preparation 19

(2R)-2-Amino-3-(indan-2-yl)propionic acid hydrochloride was prepared according to a similar manner to that of Preparation 8.

$^1\text{H NMR}(\text{D}_2\text{O}) \delta$  : 1.99-2.28(2H, m), 2.55-2.71(3H, m), 3.09-3.25(2H, m), 4.11(1H, t,  $J=6.9\text{Hz}$ ), 7.18-7.33(4H, m)

(+)APCI MS  $m/z$  : 206( $M^+ + 1$ )

#### Preparation 20

(2R)-2-tert-Butoxycarbonylamino-3-(indan-2-yl)propionic acid was prepared according to a similar manner to that of Preparation 9.

$^1\text{H NMR}(\text{CDCl}_3) \delta$  : 1.45(9H, s), 1.75-2.20(2H, m), 2.50-2.75(3H, m), 3.00-3.25(2H, m), 4.30-4.50(1H, m), 4.90-5.10(1H, m), 7.09-7.25(4H, m)

(+)APCI MS  $m/z$  : 206( $M^+ - \text{CO}_2^t\text{Bu} + 2$ )



## Preparation 21

1'-[(2R)-2-tert-Butoxycarbonylamino-3-(indan-2-yl)propionyl]-1-methanesulfonylspiro[indoline-3,4'-piperidine] was prepared according to a similar manner to that of Preparation 10.

FT IR(KBr) : 1710.6, 1641.1  $\text{cm}^{-1}$

$^1\text{H}$ NMR( $\text{CDCl}_3$ )  $\delta$  : 1.46(9H, s), 1.80-1.95(6H, m), 2.50-3.40(10H, m), 3.85-4.15(3H, m), 4.55-4.85(2H, m), 5.41(1H, d,  $J=8.9\text{Hz}$ ), 7.04-7.43(8H, m)

(+)APCI MS  $m/z$  : 454( $\text{M}^+ - \text{CO}_2^t \text{Bu} + 2$ )  
498( $\text{M}^+ - \text{C}(\text{CH}_3)_3 + 1$ )

## Preparation 22

1'-[(2R)-2-Amino-3-(indan-2-yl)propionyl]-1-methanesulfonylspiro[indoline-3,4'-piperidine] was prepared according to a similar manner to that of Preparation 11.

$^1\text{H}$ NMR( $\text{CDCl}_3$ )  $\delta$  : 1.70-2.00(6H, m), 2.50-2.90(6H, m), 2.92(3H, s), 2.95-3.35(3H, m), 3.79-4.05(4H, m), 4.50-4.80(1H, m), 7.03-7.42(8H, m)

(+)APCI MS  $m/z$  : 454( $\text{M}^+ + 1$ )

## Preparation 23

(2S)-2-tert-Butoxycarbonylamino-3-(indan-2-yl)propionic acid was prepared according to a similar manner to that of Preparation 9.

FT IR(film) : 1745.3, 1666.2, 1538.9  $\text{cm}^{-1}$

$^1\text{H}$ NMR( $\text{CDCl}_3$ )  $\delta$  : 1.45(9H, s), 1.75-2.20(2H, m), 2.50-2.75(3H, m), 3.30-3.25(2H, m), 4.30-4.50(1H, m), 4.90-5.10(1H, m), 7.09-7.25(4H, m)

(+)APCI MS  $m/z$  : 206( $\text{M}^+ - \text{CO}_2^t \text{Bu} + 2$ )

## Preparation 24

1'-[(2S)-2-tert-Butoxycarbonylamino-3-(indan-2-yl)propionyl]-1-methanesulfonylspiro[indoline-3,4'-piperidine] was prepared according to

a similar manner to that of Preparation 10.

FT IR(film) : 1745.3, 1668.1, 1538.9  $\text{cm}^{-1}$

$^1\text{H}$ NMR( $\text{CDCl}_3$ )  $\delta$  : 1.46(9H, s), 1.70-2.00(6H, m), 2.50-3.40(10H, m), 3.85-4.15(3H, m), 4.50-4.90(2H, m), 5.41(1H, d,  $J=8.9\text{Hz}$ ), 7.04-7.43(8H, m)

(+)APCI MS  $m/z$  : 454( $\text{M}^+ - \text{CO}_2^t \text{Bu} + 2$ )

498( $\text{M}^+ - \text{C}(\text{CH}_3)_3 + 1$ )

#### Preparation 25

1'-[(2S)-2-Amino-3-(indan-2-yl)propionyl]-1-methanesulfonylspiro[indoline-3,4'-piperidine] was prepared according to a similar manner to that of Preparation 11.

$^1\text{H}$ NMR( $\text{CDCl}_3$ )  $\delta$  : 1.60-2.00(6H, m), 2.50-3.40(12H, m), 3.75-4.80(5H, m), 6.95-7.45(8H, m)

(+)APCI MS  $m/z$  : 454( $\text{M}^+ + 1$ )

#### Preparation 26

Ethyl 1-[(2R)-2-amino-3-(indan-2-yl)propionyl]-3-benzylpiperidine-3-carboxylate was prepared according to similar manners to those of Preparation 10, and successively Preparation 11.

(+)APCI MS  $m/z$  : 435( $\text{M}^+ + 1$ )

#### Preparation 27

5-(1,2-Benzocyclohepten-5-yl)hydantoin (500mg) was hydrolyzed with a suspension of calcium hydroxide (1.8g) in water (20ml) at 130°C in a sealed tube for 6 hours. The insoluble material was removed by filtration. The filtrate was evaporated in vacuo to give a residue. To the residue was added acetic anhydride (0.3ml) and pyridine (5ml), and the mixture was stirred for 5 hours at ambient temperature. Evaporation of the solvent gave the residue, to which was added ethyl acetate and

water.

A pH of the mixture was adjusted to pH 1.0 with conc. hydrochloric acid. The resulting solution was partitioned between ethyl acetate and water. The organic phase was separated, washed with water, and dried over magnesium sulfate. Evaporation of the solvent gave 2-acetylamino-2-(1,2-benzocyclohepten-5-yl)acetic acid (300mg) as a white powder.

$^1\text{H NMR}(\text{CD}_3\text{OD}) \delta$  : 1.13(2H, d,  $J=5.0\text{Hz}$ ), 1.90-2.20(6H, m), 2.70-2.90(4H, m), 3.40-3.60(2H, m), 7.01-7.07(4H, m)  
(+)APCI MS  $m/z$  : 262( $\text{M}^+ + 1$ )

#### Preparation 28

2-Acetylamino-2-(1,2-benzocyclohepten-5-yl)acetic acid (300mg) was dissolved in 1N aqueous sodium hydroxide solution (20ml), and the solution was adjusted to pH 8.0 with 1N hydrochloric acid. Then the resulting mixture was allowed to warm to  $37^\circ\text{C}$ , and therein was added cobalt (II) chloride hexahydrate (1.5mg) and Acylase (Acylase Amano, 15mg). After being adjusted to pH 7.5, the reaction mixture was stirred for 24 hours, keeping the temperature at  $37^\circ\text{C}$ . To the resulting mixture was added water until insoluble material was disappeared, then the pH was adjusted to pH 1.9 with hydrochloric acid, and the resulting mixture was partitioned between ethyl acetate and water. The organic layer was separated and the aqueous layer was extracted with ethyl acetate.

The organic extracts were combined, washed successively with hydrochloric acid, water and brine, and dried over magnesium sulfate. Evaporation of the solvent gave (2R)-2-acetylamino-2-(1,2-benzocyclohepten-5-yl)acetic acid (160mg) as a foam.

(+)APCI MS  $m/z$  : 262( $\text{M}^+ + 1$ )

## Preparation 29

A suspension of (2R)-2-acetylamino-2-(1,2-benzocyclohepten-5-yl) acetic acid (140mg) in 2N hydrochloric acid (20ml) was refluxed with stirring for 6 hours. Evaporation of the solvent gave a residue, which was added to the solution of di-tert-butyl dicarbonate (94mg) in a mixture of water (10ml) and dioxane (10ml). To the solution was added triethylamine (0.16ml) at room temperature. After stirring 18 hours, the solvent was removed under a reduced pressure. The residue was dissolved in water and therein was added ethyl acetate. The resulting mixture was adjusted to pH 2.0 with 2N hydrochloric acid. The organic layer was separated, washed with 0.1N hydrochloric acid and brine, and dried over magnesium sulfate.

Evaporation of the solvent gave (2R)-2-tert-butoxycarbonylamino-(1,2-benzocyclohepten-5-yl)acetic acid (30mg) as a form.

$^1\text{H NMR}(\text{CDCl}_3) \delta$  : 1.20-1.27(2H, m), 1.38(9H, s), 1.83-2.21(3H, m), 2.70-2.80(4H, m), 4.10-4.24(1H, m), 5.11-5.14(1H, m), 7.00-7.10(4H, m)

## Preparation 30

1-Ethyl-3-(3'-dimethylaminopropyl)carbodiimide (21  $\mu$ l) was added to a mixture of (2R)-2-t-butoxycarbonylamino-2-(1,2-benzocyclohepten-5-yl) acetic acid (27mg), 1-methanesulfonylspiro[indoline-3,4'-piperidine] hydrochloride (28mg), and 1-hydroxybenzotriazole (15mg) in dichloromethane (20ml) at ambient temperature and the resulting mixture was stirred at the same temperature overnight.

The reaction mixture was partitioned between ethyl acetate and water. The organic layer was separated, washed with water and brine, dried over magnesium sulfate, and concentrated in vacuo to give residue.

Trifluoro acetic acid (1ml) was added to a solution of the residue

in dichloromethane (10ml) at ambient temperature, and the mixture was stirred for 4 hours. The reaction mixture was concentrated in vacuo and partitioned between ethyl acetate and a saturated solution of sodium hydrogen carbonate in water. The organic layer was separated, washed with water and brine, dried over magnesium sulfate, and evaporated to dryness to give (2R)-1-[2-amino-2-(1,2-benzocyclohepten-5-yl)acetyl]-1-methanesulfonylspiro[indoline-3,4'-piperidine] (30mg) as a powder.

$^1\text{H NMR}(\text{CDCl}_3) \delta$  : 1.40-2.15(13H, m), 2.70-3.00(7H, m), 3.60-4.10(3H, m), 4.60-4.80(2H, m), 6.93-7.66(8H, m)  
(+)APCI MS  $m/z$  : 468( $M^+$  +1)

#### Preparation 31

A 0.95M solution of diisobutylaluminium hydride in n-hexane(213ml) was added dropwise to a stirred solution of ethyl 3,4-dihydronaphthalene-2-carboxylate(20.48g) in toluene(400ml) at -70 to -50°C in the presence of atmospheric  $\text{N}_2$  gas over 30 minutes. The resulting mixture was stirred at the same temperature for 2 hours, allowed to stand at room temperature overnight, and added dropwise to stirred 2N hydrochloric acid(100ml) under ice cooling over 30 minutes. The organic layer was separated, washed with a 20% aqueous solution of potassium sodium tartrate, aqueous sodium bicarbonate, and brine, dried over magnesium sulfate, and evaporated in vacuo to give 3,4-dihydronaphthalene -2-methanol(8.24g) as an oil.

IR(film); 3336, 2927, 2881, 2833, 1485, 1446  $\text{cm}^{-1}$

$^1\text{H NMR}(\text{DMSO}-d_6) \delta$  ; 2.16(2H, t,  $J=8.15\text{Hz}$ ), 2.74(2H, m), 4.02(2H, d,  $J=5.3\text{Hz}$ ) 4.95(1H, t,  $J=5.3\text{Hz}$ ), 6.40(1H, s), 7.01-7.16(4H, m)

(+)APCI MS  $m/z$ ; 159( $M^+$ +1)

#### Preparation 32

Thionyl chloride(6.8ml) was added dropwise to a stirred solution of 3,4-dihydronaphthalene-2-methanol(5.0g) in methylene chloride(100ml) at 0°C. The resulting mixture was stirred at room temperature for 5 hours and evaporated in vacuo. The residue was extracted with ethyl acetate. The extract was washed with water(three times) and brine, dried over magnesium sulfate, and evaporated in vacuo to afford 2-chloromethyl-3, 4-dihydronaphthalene(5.4g) as an oil.

<sup>1</sup>H NMR(DMSO-d<sub>6</sub>) δ : 2.33(2H, t, J=8.20Hz), 2.80(2H, m), 4.39(2H, s), 6.63(1H, s), 7.06-7.19(4H, m)  
(+)APCI MS m/z; 143(M<sup>+</sup>-Cl)

### Preparation 33

A 1.0M solution of Lithium bis(trimethylsilyl) amide in tetrahydrofuran(31.7ml) was added dropwise to a stirred solution of N-diphenylmethylideneglycine methyl ester(7.65g) in tetrahydrofuran(180ml) at -70°C and then a solution of 2-chloromethyl-3, 4-dihydronaphthalene(5.4g) in tetrahydrofuran(50ml) was added dropwise therein at the same temperature. The resulting mixture was allowed to room temperature and stirred for 4 hours. 2N hydrochloric acid(75.5ml) was added dropwise to the mixture at 0°C. Evaporation of the tetrahydrofuran gave the residue, which was washed with ethyl acetate. The Aqueous layer was evaporated in vacuo. The residue was added to 2N hydrochloric acid(100ml), then the resulting mixture was refluxed for 3 hours and washed with ethyl acetate. Evaporation of the water gave 2-amino-3-(3, 4-dihydronaphthalen-2-yl) propionic acid hydrochloride(9.8g) as a solid.

IR(NaCl); 3133, 1739, 1404, 1226 cm<sup>-1</sup>

<sup>1</sup>H NMR(D<sub>2</sub>O) δ : 2.32(2H, t, J=8.10), 2.74-2.99(4H, m), 4.24(1H, dd, J=5.5, 8.3Hz), 6.47(1H, s), 7.13-7.24(4H, m)

(+)APCI MS m/z; 218(M<sup>+</sup>+1)

## Preparation 34

To a solution of 2-amino-3-(3, 4-dihydronaphthalen-2-yl) propionic acid hydrochloride(9.64g) in a mixture of water(100ml) and 1, 4-dioxane (100ml) was added di-tert-butylidicarbonate(7.28g) and triethylamine(5.3ml), and the resulting mixture was stirred for 18 hours at ambient temperature. Evaporation of the solvent gave a residue, which was acidified to pH2 with 1N hydrochloric acid, and extracted twice with ethyl acetate. The extracts were combined, dried over magnesium sulfate, and evaporated in vacuo to give 2-t-butoxycarbonylamino-3-(3, 4-dihydronaphthalen -2-yl) propionic acid(7.38g) as a solid.

IR(KBr); 3336, 3068, 1755, 1664, 1533  $\text{cm}^{-1}$

$^1\text{H}$  NMR( $\text{MeOH}-d_4$ ); 1.37(9H, s), 2.25-2.82(6H, m), 4.35(1H, q,  $J=5.0\text{Hz}$ ) 6.29(1H, s), 6.93-7.10(4H, m)

## Preparation 35

1-Ethyl-3-(3-dimethylaminopropyl)carbodiimide(0.46ml) was added to a mixture of 2-t-butoxycarbonylamino-3-(3, 4-dihydronaphthalen -2-yl) propionic acid(464mg), 1-methanesulfonylspiro[indoline-3, 4'-piperidine] hydrochloride(500mg) and 1-hydroxybenzotriazole(267mg) in dichloromethane(20ml) at ambient temperature and the resulting mixture was stirred at the same temperature overnight.

The reaction mixture was partitioned between ethyl acetate and water. The organic layer was separated, washed with water, brine, and dried over magnesium sulfate, and evaporated in vacuo to give 1'-[2-(tert-butoxycarbonylamino)-3-(3, 4-dihydronaphthalen -2-yl) propionyl]-1-methanesulfonylspiro[indoline-3, 4'-piperidine](780mg) as a foam.

IR(film); 1706, 1639, 1479, 1456, 1350, 1161  $\text{cm}^{-1}$

$^1\text{H}$  NMR( $\text{CDCl}_3$ )  $\delta$ ; 1.40(9H, s), 1.70-1.95(6H, m), 2.23-2.53(5H, m), 2.6,

and 2.7(3H, each s), 3.22(1H, m), 3.80, and 3.88(2H, each s), 4.07(1H, m), 4.61-4.69(1H, br-d J=13.8Hz, 4.87(1H, m), 5.32(1H, m), 6.28, 6.33, 6.39, and 6.42(1H, each s), 6.38-6.42 and 6.84-7.42(8H, m)

(+)APCI MS m/z;566(M<sup>+</sup>+1)

#### Preparation 36

Trifluoroacetic acid(4ml) was added to a solution of 1'-[2-(tert-butoxycarbonylamino)-3-(3, 4-dihydronaphthalen -2-yl) propionyl]-1-methanesulfonylspiro[indoline-3, 4'-piperidine](780mg) in dichloromethane (20ml) at ambient temperature and the resulting mixture was stirred at the same temperature overnight.

The reaction mixture was evaporated in vacuo and partitioned between ethyl acetate and saturated sodium hydrogen carbonate in water. The organic layer was separated, washed with water and brine, dried over magnesium sulfate, and evaporated in vacuo to give 1'-[2-amino-3-(3, 4-dihydronaphthalen -2-yl) propionyl]-1-methanesulfonylspiro[indoline-3, 4'-piperidine](520mg) as a foam.

IR(film); 2925, 1635, 1471, 1344, 1159 cm<sup>-1</sup>

<sup>1</sup>H NMR(CDC1<sub>3</sub>) δ; 1.72-2.84(1H, m), 2.88-2.90(3H, each s), 3.21(1H, m), 3.84-4.18(4H, m), 4.66(1H, m), 6.36(1H, s), 6.51-6.55 and 6.91-7.38(8H, m)

(+)APCI MS m/z ;466(M<sup>+</sup>+1)

#### Preparation 37

Sodium borohydride(2.37g) was added to a stirred solution of 5-oxo-1, 2-benzocycloheptene-6-carboxylic acid ethyl ester(7.3g) in methanol at 0°C. The resulting mixture was allowed to stand at room temperature for 2 hours, added dropwise to stirred 1N hydrochloric acid under ice cooling over 30 minutes, and extracted twice with ethyl



acetate. The extracts were combined, washed with saturated sodium hydrogen carbonate and brine, dried over magnesium sulfate, and evaporated in vacuo to give 5-hydroxy-1, 2-benzocycloheptene -6-carboxylic acid ethyl ester(7.11g) as an oil.

FTIR(Neat) ; 3473, 2929, 1722, 1448, 1261, 1184  $\text{cm}^{-1}$

$^1\text{H}$  NMR( $\text{CDCl}_3$ )  $\delta$  ; 1.25(3H, m), 2.01(3H, m), 2.31-2.79(4H, m), 3.60(1H, d,  $J=5\text{Hz}$ ), 4.08-4.26(2H, m), 5.07(1H, s), 7.07-7.64(4H, m)

#### Preparation 38

A solution of 5-hydroxy-1, 2-benzocycloheptene -6-carboxylic acid ethyl ester(7.11g) and p-toluenesulfonic acid monohydrate(570mg) in toluene(140ml) was refluxed for 2 hours and added dropwise to stirred 1N hydrochloric acid under ice cooling over 30 minutes. The organic layer was washed with 1N hydrochloric acid, water, saturated sodium hydrogen carbonate, and brine, dried over magnesium sulfate, and evaporated in vacuo to give 2-benzo-1, 3-cycloheptadiene-4-carboxylic acid ethyl ester (6.32g) as an oil.

IR(neat) ; 1703, 1448, 1290, 1240, 1198  $\text{cm}^{-1}$

$^1\text{H}$  NMR( $\text{CDCl}_3$ )  $\delta$  ; 1.35(3H, t,  $J=7.1\text{Hz}$ ), 2.00-2.11(2H, m) 2.24(1H, m) 2.63(1H, t,  $J=5.8\text{Hz}$ ), 2.82(2H, t,  $J=5.9\text{Hz}$ ), 4.27(2H, q,  $J=7.1\text{Hz}$ ), 7.10-7.34(4H, m), 7.70(1H, s)

#### Preparation 39

4-Hydroxy methyl-1, 2-benzo-1, 3-cycloheptadiene was prepared from 1, 2-benzo-1, 3-cycloheptadiene-4-carboxylic acid ethyl ester in a similar manner to Preparation 31.

$^1\text{H}$  NMR( $\text{CDCl}_3$ )  $\delta$  ; 1.97-2.09(2H, m), 2.36(2H, t), 2.78-2.84(2H, m) 4.21(2H, s), 6.52(1H, s), 7.10-7.26(4H, m)

(+)APCI MS  $m/z$  ;157( $\text{M}^+-\text{OH}$ )

## Preparation 40

4-Chloromethyl-1, 2-benzo-1, 3-cycloheptadiene was prepared from 4-hydroxy methyl-1, 2-benzo-1, 3-cycloheptadiene in a similar manner to Preparation 32.

$^1\text{H}$  NMR( $\text{CDCl}_3$ )  $\delta$  ; 1.64-2.33(4H, m), 2.44-2.51(2H, m), 4.21(2H, s), 6.58(1H, s), 7.08-7.16(4H, m)

(+)APCI MS  $m/z$  ;157( $\text{M}^+-\text{Cl}$ )

## Preparation 41

2-Amino-3-(1, 2-benzo-1, 3-cycloheptadien-4-yl)propionic acid hydrochloride was prepared from 4-chloromethyl-1, 2-benzo-1, 3-cycloheptadiene in a similar manner to Preparation 33.

$^1\text{H}$  NMR( $\text{Me}_2\text{OD}-d_3$ )  $\delta$  ; 2.04(2H, m), 2.37(2H, m), 2.69(1H, m) 2.85(3H, m), 4.07(1H, dd,  $J=5.4\text{Hz}$ ,  $J=8.9\text{Hz}$ ), 6.46(1H, s), 7.08-7.14(4H, m)

## Preparation 42

2-tert-Butoxycarbonylamino-3-(1, 2-benzo-1, 3-cycloheptadien-4-yl) propionic acid was prepared from 2-amino-3-(1, 2-benzo-1, 3-cycloheptadien-4-yl) propionic acid hydrochloride in a similar manner to Preparation 34.

$^1\text{H}$  NMR( $\text{CDCl}_3$ )  $\delta$  ; 1.41(9H, s), 2.05(2H, m), 2.31-2.78(6H, m), 5.00-5.50(1H, m), 6.34(1H, s), 7.09-7.13(4H, m)

## Preparation 43

1'-[2-tert-Butoxycarbonylamino-3-(1, 2-benzo-1, 3-cycloheptadien-4-yl) propionyl]-1-methanesulfonylspro[indoline-3, 4'-piperidine] was prepared from 2-tert-butoxycarbonylamino-3-(1, 2-benzo-1, 3-cycloheptadien-4-yl)propionic acid in a similar manner to Preparation

35.

$^1\text{H}$  NMR( $\text{CDCl}_3$ )  $\delta$  ; 1.45(9H, s), 1.64-1.96(8H, m), 2.05-2.78(5H, m), 2.91(3H, m), 2.93-3.18(1H, m), 3.83(2H, s), 4.01(1H, m), 4.65(1H, m), 4.88(1H, m), 5.37(1H, m), 6.32(1H, m), 7.10-7.42(8H, m)

## Preparation 44

1'-[2-Amino-3-(1, 2-benzo-1, 3-cycloheptadien-4-yl)propionyl]-1-methanesulfonylspiro[indoline-3, 4'-piperidine] was prepared from 1'-[2-(tert-butoxycarbonylamino)-3-(1, 2-benzo-1, 3-cycloheptadien-4-yl)propionyl]-1-methanesulfonylspiro[indoline-3, 4'-piperidine] in a similar manner to Preparation 36.

IR(KBr) ; 3735, 1625, 1452, 1338, 1228, 1149  $\text{cm}^{-1}$

$^1\text{H}$  NMR( $\text{CDCl}_3$ )  $\delta$  ; 1.71-2.80(13H, m), 2.89, 2.91(3H, each s), 3.20(1H, m), 3.82-4.17(4H, m), 4.67(1H, m), 6.38(1H, m), 6.85 and 7.12-7.37(8H, m)  
(+)APCI MS  $m/z$  ;480( $M^+2$ )

## Preparation 45

To a solution of oxalyl chloride(2.05ml) in dichloromethane(170ml) was added dropwise in turn with dimethylsulfoxide(3.22ml), 2-hydroxymethylindan(2.92g) and triethylamine(13.7ml) at  $-70^\circ\text{C}$  under nitrogen atmosphere. The reaction mixture was allowed to warm to ambient temperature and the precipitate was removed by filtration. The filtrate was concentrated to give a residue, which was dissolved in ethyl acetate, washed in turn with water, 1N hydrochloric acid, brine, a saturated sodium hydrogencarbonate solution in water, and brine, and dried over magnesium sulfate. Evaporation of the solvent gave a residue, which was chromatographed on silica gel eluting with 10% ethyl acetate in n-hexane to give 2-formylindan (2.63g) as an oil.

$^1\text{H}$  NMR( $\text{CDCl}_3$ )  $\delta$  ; 3.12-3.35(5H, m), 7.17-7.26(4H, m), 9.77(1H, s)

## Preparation 46

A stirred suspension of 2-formylindan(2.63g), sodium cyanide(2.65g), and ammonium carbonate(14g) in a mixture of methanol(30ml) and water(30ml) was refluxed for 18 hours. Methanol was evaporated in vacuo, and the remaining was allowed to 0°C and stirred for 3 hours. The insoluble material was collected by filtration, washed with water and dried to give 5-(2-indanyl) imidazolidine-2, 4-dione(1.25g) as a solid.

<sup>1</sup>H NMR(DMSO-d<sub>6</sub>) δ; 2.70-3.04(5H, m), 4.18-4.22(1H, m), 7.09-7.20(4H, m), 8.07(1H, s), 10.69(1H, s)

(+)APCI MS m/z ;217(M<sup>+</sup>+1)

## Preparation 47

5-(2-indanyl)imidazolidine-2, 4-dione(1.25g) was hydrolyzed with a suspension of calcium hydroxide(4.46g) in water(50ml) at 130°C in a sealed tube for 6 hours.

Insoluble material was removed by filtration. To the filtrate was added di-tert-butylidicarbonate(981mg), triethylamine(1.5ml), and 1,4-dioxane(30ml), and the mixture was stirred for 18 hours at ambient temperature. Evaporation of the solvent gave a residue, which was acidified to pH2 with 1N hydrochloric acid and extracted twice with ethyl acetate. The extracts were combined, dried over magnesium sulfate, and evaporated in vacuo to give 2-tert-butoxycarbonylamino-(2-indanyl) acetic acid(330mg) as an oil.

<sup>1</sup>H NMR(CDCl<sub>3</sub>) δ; 1.44(9H, s), 2.69-3.66(4H, m), 4.40-4.50(1H, m) 5.00-5.10(1H, m), 7.10-7.19(4H, m)

## Preparation 48

1-Ethyl-3-(3-dimethylaminopropyl)carbodiimide(0.24ml) was added to

a mixture of 2-tert-butoxycarbonylamino-(2-indanyl)acetic acid(300mg), 1-methanesulfonylspiro[indoline-3, 4'-piperidine]hydrochloride(312mg), and 1-hydroxybenzotriazole(167mg) in dichloromethane(10ml) at an ambient temperature and the resulting mixture was stirred at the same temperature overnight.

The reaction mixture was partitioned between ethyl acetate and water. The organic layer was separated, washed with water and brine, dried over magnesium sulfate, and evaporated in vacuo to give a residue.

Trifluoroacetic acid(1ml) was added to a solution of the residue in dichloromethane(10ml) at ambient temperature and the mixture was stirred for 4 hours. The reaction mixture was evaporated in vacuo and partitioned between ethyl acetate and a saturated solution of sodium hydrogen carbonate in water. The organic layer was separated, washed with water and brine, dried over magnesium sulfate, and evaporated in vacuo to give 1'-[2-amino-2-(2-indanyl)acetyl]-1-methanesulfonylspiro[indoline-3, 4'-piperidine](350mg) as a powder.

<sup>1</sup>H NMR(CDCl<sub>3</sub>) δ ; 1.52-2.00(4H, m), 2.10-3.21(12H, m), 3.86-4.10(4H, m), 4.60-4.70(1H, m), 7.03-7.37(8H, m)

(+)APCI MS m/z ;440(M<sup>+</sup>+1)

#### Preparation 49

1-[(2R)-2-amino-3-(2-indanyl)propionyl]-4-(2-keto-1-benzimidazoliny)l)piperidine was prepared from (2R)-2-tert-butoxycarbonylamino-3-(indan-2-yl)propionic acid in a similar manner to Preparation 48.

<sup>1</sup>H NMR(CDCl<sub>3</sub>) δ ; 1.65-2.00(6H, m), 2.10-2.75(5H, m), 3.00-3.25(3H, m) 3.80-3.92(1H, m), 4.00-4.10(1H, m), 4.50-4.60(1H, m), 4.80-4.95(2H, m), 6.80-7.26(8H, m), 9.64(1H, br-s)

APCI MS m/z ;405(M<sup>+</sup>+1)

## Preparation 50

To a solution of methyl 2-acetylamino-2-(dimethoxyphosphoryl) acetate(1.51g) in acetonitrile(20ml) was added 1, 8-diazabicyclo[5. 4. 0]undec-7-ene (0.85ml). After 10 minutes, 5-formyl-1, 2-benzocycloheptene(1.0g) was added and the resulting mixture was stirred for 2 days at room temperature. The solution is diluted with ethyl acetate, washed with 1N sulfuric acid, dried, and concentrated under vacuum. The residue was filtered through silica gel (hexane / ethyl acetate 1:1) to give 2-acetylamino-3-(1, 2-benzocyclohepten-5-yl)-2-propenoic acid methyl ester(460mg) as a solid.

<sup>1</sup>H NMR(CDCl<sub>3</sub>) δ ; 1.20-1.38(2H, m), 2.00-2.10(2H, m), 2.17(3H, s) 2.70-2.90(5H, m), 3.76(3H, s), 6.50(1H, d, J=10.4Hz) 7.05-7.15(4H, m)

APCI MS m/z ;288(M<sup>+</sup>+1)

## Preparation 51

A mixture of 2-acetylamino-3-(1, 2-benzocyclohepten-5-yl)-2-propenoic acid methyl ester(460mg) and 10% Pd/C(100mg)in methanol(10ml) was stirred in the presence of an atmospheric hydrogen for 2 hours at room temperature and filtered.

The filtrate was evaporated in vacuo to give 2-acetylamino-3-(1, 2-benzocyclohepten-5-yl)propionic acid methyl ester(460mg) as a solid.

<sup>1</sup>H NMR(CDCl<sub>3</sub>) δ ; 1.10-1.30(2H, m), 1.48-2.05(8H, m), 2.70-2.89(4H, m), 3.74(3H, s), 4.70(1H, t-d, J=8, 4.7Hz), 5.87(1H, d, J=8.0Hz), 7.00-7.10(4H, m)

APCI MS m/z ;290(M<sup>+</sup>+1)

## Preparation 52

A stirred suspension of 2-acetylamino-3-(1, 2-benzocyclohepten-5-

yl)propionic acid methyl ester(460mg) in 2N hydrochloric acid (20ml). The solvent was evaporated in vacuo. Di-tert-butyldicarbonate(320mg) and triethylamine(1.5ml) was added to a solution of the residue in a mixture of water (5ml) and 1,4-dioxane(5ml), and the mixture was stirred for 18 hours at room temperature. Evaporation of the solvent gave a residue, which was acidified to pH2 with 1N hydrochloric acid, and extracted twice with ethyl acetate. The extracts were combined, dried over magnesium sulfate, and evaporated in vacuo to give 2-tert-butoxycarbonylamino-3-(1, 2-benzocyclohepten-5-yl)propionic acid(520mg) as a solid.

<sup>1</sup>H NMR(CDCl<sub>3</sub>) δ ; 1.00-2.10(16H, m), 2.60-2.80(4H, m), 4.30-4.45(1H, m), 4.90-4.95(1H, m), 7.00-7.15(4H, m)

#### Preparation 53

1'-[2-Amino-3-(1, 2-benzocyclohepten-5-yl)propionyl]-1-methanesulfonylspiro[indoline-3, 4'-piperidine]was prepared from 2-tert-butoxycarbonylamino-3-(1, 2-benzocyclohepten-5-yl)propionic acid in a similar manner to Preparation 48.

<sup>1</sup>H NMR(CDCl<sub>3</sub>) δ ; 1.20-3.40(22H, m) 3.87-4.14(4H, m), 4.59-4.65(1H, m), 7.09-7.41(8H, m)

APCI MS m/z ;482(M<sup>+</sup>+1)

#### Example 1

1-Ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (885mg) was added to a solution of 1'-[2-amino-3-(indan-2-yl)propionyl]-1-methanesulfonylspiro[indoline-3, 4'-piperidine](1.4g), N-tert-butoxycarbonyl- $\alpha$ -methylalanine(700mg) and 1-hydroxybenzotriazole(486mg) in dichloromethane(30ml) at ambient temperature, and the resulting mixture was stirred at the same temperature overnight. The reaction

mixture was partitioned between ethyl acetate and water. The organic layer was washed with water and brine, dried over magnesium sulfate, and evaporated in vacuo. The residue was chromatographed (n-hexane-ethyl acetate) over silica gel to afford N-[1-[(1-methanesulfonylspiro[indoline-3,4'-piperidine]-1'-yl)carbonyl]-2-(indan-2-yl)ethyl]-2-tert-butoxycarbonylamino-2-methylpropanamide (1.64g).

IR(KBr); 2933, 1716, 1637, 1506, 1470, 1454, 1350, 1252, 1161  $\text{cm}^{-1}$ .

$^1\text{H}$  NMR( $\text{CDCl}_3$ )  $\delta$ : 1.40-1.15(15H, m), 1.65-2.10(6H, m), 2.40-3.40(10H, m), 3.80-4.20(3H, m), 4.50-4.70(1H, m), 4.94(1H, s), 5.00-5.20(1H, m).  
(+)APCI MS  $m/z$ ; 639( $M^+ + 1$ ).

#### Example 2

A suspension of N-[1-[(1-methanesulfonylspiro[indoline-3,4'-piperidine]-1'-yl)carbonyl]-2-(indan-2-yl)ethyl]-2-tert-butoxycarbonylamino-2-methylpropanamide (1.5g) in 4N-hydrogen chloride in ethyl acetate (5ml) was stirred at ambient temperature for 9 hours and evaporated in vacuo. The residue was powdered from ethyl acetate and the powder was washed with diethyl ether to afford 2-amino-N-[1-[(1-methanesulfonylspiro[indoline-3,4'-piperidine]-1'-yl)carbonyl]-2-(indan-2-yl)ethyl]-2-methylpropanamide hydrochloride.

mp: 185.4-187.0  $^{\circ}\text{C}$

IR(KBr); 2850, 1670, 1629, 1539, 1471, 1342, 1157  $\text{cm}^{-1}$ .

$^1\text{H}$  NMR( $\text{CD}_3\text{OD}$ )  $\delta$ : 1.60-2.10(13H, m), 2.40-3.50(9H, m), 3.90-4.20(3H, m), 4.40-4.65(1H, m), 4.95-5.10(1H, m), 7.03-7.40(8H, m),  
(+)APCI MS  $m/z$ ; 539( $M^+ + 1$ ).

#### Example 3

1-Ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (283mg) was added to a solution of 1'-[2-amino-2-(1,2-benzocyclohepten-5-yl)]



acetyl]-1-methanesulfonylspiro[indoline-3,4'-piperidine] (450mg), N-tert-butoxycarbonyl- $\alpha$ -methylalanine (224mg), and 1-hydroxybenzotriazole (156mg) in dichloromethane (10ml) at an ambient temperature, and the resulting mixture was stirred at the same temperature overnight. The reaction mixture was partitioned between ethyl acetate and water. The organic layer was washed with water and brine, dried over magnesium sulfate. Evaporation of the solvent gave a residue, which was chromatographed (n-hexane-ethyl acetate) over silica gel to afford N-[[1-(1,2-benzocyclohepten-5-yl)-2-oxo-2-(1-methanesulfonylspiro[indoline-3,4'-piperidine]-1'-yl)]ethyl]-2-tert-butoxycarbonylamino-2-methylpropanamide (444mg).

FT IR(KBr) : 2979, 2931, 1722, 1714, 1641, 1631, 1454, 1348, 1161  $\text{cm}^{-1}$

$^1\text{H NMR}(\text{CDCl}_3) \delta$  : 1.36-1.48(15H, m), 1.54-1.99(8H, m), 2.61-2.78(6H, m), 2.92(3H, s), 3.20-3.23(1H, m), 3.87-3.96(2H, m), 4.00-4.10(1H, m), 4.62-4.68(2H, m), 4.8-4.90(2H, m), 7.03-7.60(8H, m)

(+)APCI MS  $m/z$  : 653( $M^+ + 1$ )

#### Example 4

A suspension of N-[[1-(1,2-benzocyclohepten-5-yl)-2-oxo-2-(1-methanesulfonylspiro[indoline-3,4'-piperidine]-1'-yl)]ethyl]-2-tert-butoxycarbonylamino-2-methylpropanamide (444mg) in 4N hydrogen chloride in ethyl acetate (3ml) was stirred at ambient temperature for 5 hours and evaporated in vacuo to give a residue.

The residue was powdered from ethyl acetate and the powder was washed with diethyl ether to afford 2-amino-N-[[1-(1,2-benzocyclohepten-5-yl)-2-oxo-2-(1-methanesulfonylspiro[indoline-3,4'-piperidine]-1'-yl)]ethyl]-2-methylpropanamide hydrochloride (300mg).

FT IR(KBr) : 2929, 1678, 1639, 1628, 1514, 1479, 1454, 1346, 1159  $\text{cm}^{-1}$

$^1\text{H NMR}(\text{CD}_3\text{OD}) \delta$  : 1.57-1.60(6H, m), 1.62-2.32(9H, m), 2.82-2.86(6H, m), 2.97

(3H, s), 3.32-3.36(1H, m), 3.94-4.11(3H, m), 4.55-4.60(1H, m), 7.07-7.56(8H, m)

#### Example 5

N-[2-[(1-methanesulfonylspiro[indoline-3,4'-piperidine]-1'-yl)carbonyl]-indan-2-yl]-2-amino-2-methylpropanamide hydrochloride was prepared according to similar manners to those of Example 1, and successively Example 2.

LD MS m/z : 533 ( $M^+$  +1+Na)

#### Example 6

N-[(1R)-1-[(1-Methanesulfonylspiro[indoline-3,4'-piperidine]-1'-yl)carbonyl]-2-(indan-2-yl)ethyl]-2-tert-butoxycarbonylamino-2-methylpropanamide was prepared according to a similar manner to that of Example 1.

FT IR(KBr) : 1710.6, 1675.8, 1641.3, 1511.9, 1483.0  $\text{cm}^{-1}$

$^1\text{H NMR}(\text{CDCl}_3) \delta$  : 1.40-2.05(21H, m), 2.45-3.35(10H, m), 3.80-4.20(3H, m), 4.45-4.70(1H, m), 4.91(1H, br. s), 5.00-5.20(1H, m), 7.00-7.45(8H, m)

(+)APCI MS m/z : 539( $M^+$  - $\text{CO}_2^t$  Bu+2)

583( $M^+$  - $\text{C}(\text{CH}_3)_3$ +1)

#### Example 7

2-Amino-N-[(1R)-1-[(1-methanesulfonylspiro[indoline-3,4'-piperidine]-1'-yl)carbonyl]-2-(indan-2-yl)ethyl]-2-methylpropanamide hydrochloride was prepared according to a similar manner to that of Example 2.

$^1\text{H NMR}(\text{CD}_3\text{OD}) \delta$  : 1.60-2.10(13H, m), 2.40-3.50(9H, m), 3.90-4.20(3H, m), 4.40-4.65(1H, m), 4.95-5.10(1H, m), 7.00-7.40(8H, m)

(+)APCI MS m/z : 539( $M^+$  +1)

## Example 8

N-[(1S)-1-[(1-Methanesulfonylspiro[indoline-3,4'-piperidine]-1'-yl)carbonyl]-2-(indan-2-yl)ethyl]-2-tert-butoxycarbonylamino-2-methylpropanamide was prepared according to a similar manner to that of Example 1.

FT IR(film) : 1706.7, 1641.1, 1511.9  $\text{cm}^{-1}$

$^1\text{H NMR}(\text{CDCl}_3) \delta$  : 1.40-2.05(21H, m), 2.45-3.35(10H, m), 3.80-4.20(3H, m), 4.45-4.70(1H, m), 4.93(1h, br. s), 5.00-5.20(1H, m), 7.00-7.45(8H, m)

(+)APCI MS m/z : 539( $\text{M}^+ - \text{CO}_2^t \text{Bu} + 2$ )

## Example 9

2-Amino- N-[(1S)-1-[methanesulfonylspiro[indoline-3,4'-piperidine]-1'-yl)carbonyl]-2-(indan-2-yl)ethyl]-2-methylpropanamide hydrochloride was prepared according to a similar manner to that of Example 2.

$^1\text{H NMR}(\text{CD}_3\text{OD}) \delta$  : 1.60-2.10(13H, m), 2.40-3.50(9H, m), 3.90-4.20(3H, m), 4.40-4.65(1H, m), 4.95-5.10(1H, m), 7.00-7.40(8H, m)

(+)APCI MS m/z : 539( $\text{M}^+ + 1$ )

## Example 10

1-Ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride(31mg) was added to a stirred mixture of 1'[2-amino-3-indan-2-yl)propionyl]-1-methanesulfonylspiro[indoline-3,4'-piperidine](48mg), 1-hydroxybenzotriazole(17mg) in dichloromethane(5ml). After stirring for 4 hours, the reaction mixture was evaporated and the residue was partitioned between ethyl acetate and water. The organic layer was separated, washed by turns with 0.1N hydrochloric acid, brine, a saturated solution of sodium hydrogen carbonate in water, and brine (twice), and dried over magnesium sulfate. Evaporation of the solvent gave a residue,

which was chromatographed on silica gel eluting with a mixture of n-hexane and ethyl acetate. Active fractions were combined and concentrated in vacuo to give a foam.

A solution to this material in 4N hydrogen chloride in ethyl acetate (5ml) was stirred for 2 hours at ambient temperature. The reaction mixture was evaporated and azeotroped three times with ethyl acetate to give a powder. The powder was collected, washed with ethyl ether, and dried in vacuo to give N-[1-(indan-2-ylmethyl)-2-oxo-2-(1-methanesulfonylspiro[indoline-3,4'-piperidine]-1'-yl)ethyl]-4-piperidinecarboxamide hydrochloride (50mg)

$^1\text{H NMR}(\text{CD}_3\text{OD}) \delta$  : 1.75-2.25(12H, m), 2.40-3.50(13H, m), 3.90-4.20(3H, m), 4.40-4.65(1H, m), 4.90-5.10(1H, m), 7.00-7.45(8H, m).

(+)APCI MS m/z; 565( $M^+ + 1$ )

#### Example 11

Ethyl 1-[(2R)-2-Amino-2-methylpropionylamino-3-(indan-2-yl)propionyl]-3-benzylpiperidine-3-carboxylate hydrochloride was prepared according to similar manners to those of Example 1, and successively Example 2.

$^1\text{H NMR}(\text{CD}_3\text{OD})$  (mixture of rotamers)  $\delta$  : 1.03-5.20(29H, m), 7.00-7.30(9H, m)

(+)APCI MS m/z : 520( $M^+ + 1$ )

#### Example 12

1-Ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (19mg) was added to a solution of (2R)-1'-[2-amino-2-(1,2-benzocyclohepten-5-yl)acetyl]-1-methanesulfonylspiro[indoline-3,4'-piperidine] (30mg), N-tert-butoxycarbonyl- $\alpha$ -methylalanine (15mg), and 1-hydroxybenzotriazole (10.4mg) in dichloromethane (10ml) at ambient temperature, and the resulting mixture was stirred at the same temperature overnight. The

reaction mixture was partitioned between ethyl acetate and water. The organic layer was washed with water and brine, dried over magnesium sulfate, and concentrated in vacuo. The residue was chromatographed (n-hexane-ethyl acetate) over silica gel, and active fractions were concentrated in vacuo to give a foam.

A suspension of the foam in 4N hydrogen chloride in ethyl acetate (5ml) was stirred at ambient temperature for 5 hours, and evaporated to dryness. The residue was powdered from ethyl acetate and the powder was washed with diethyl ether to afford (1R)-2-Amino-N-[[1-(1,2-benzocyclohepten-5-yl)-2-oxo-2-(1-methanesulfonylspiro[indoline-3,4'-piperidine]-1'-yl)]ethyl]-2-methylpropanamide hydrochloride (28mg) as a solid.

FT IR(KBr) : 2929, 1674, 1624, 1523, 1477, 1458, 1346, 1159  $\text{cm}^{-1}$

$^1\text{H NMR}(\text{CD}_3\text{OD}) \delta$  : 1.46-1.61(6H, m), 1.82-2.32(9H, m), 2.83-3.01(9H, m), 3.30-3.36(1H, m), 3.90-4.60(4H, m), 7.06-7.40(8H, m)

(+)APCI MS  $m/z$  : 553( $\text{M}^+ + 1$ )

### Example 13

1 - Ethyl - 3 - ( 3 - dimethylaminopropyl ) carbodiimide hydrochloride (255mg) was added to a solution 1' - [ 2 - amino - 3 - ( 3 , 4 - dihydronaphthalen - 2 - yl ) propionyl ] - 1 - methanesulfonylspiro [ indoline - 3 , 4' - piperidine ] (520mg), N - tert - butoxycarbonyl -  $\alpha$  - methylalanine ( 255mg ) , and 1 - hydroxybenzotriazole (182mg) in dichloromethane (20ml) at ambient temperature, and the resulting mixture was stirred at the same temperature overnight.

The reaction mixture was partitioned between ethyl acetate and water. The organic layer was washed with water and brine, dried over magnesium sulfate, and evaporated in vacuo. The residue

was chromatographed (n-hexane-ethyl acetate) over silica gel to afford N-[1-[(1-methanesulfonylspiro[indoline-3,4'-piperidine]-1'-yl) carbonyl]-2-(3,4-dihydronaphthalen-2-yl) ethyl]-2-[(tert-butoxycarbonyl) amino]-2-methylpropanamide (740mg) as a foam.

<sup>1</sup>H NMR (CDCl<sub>3</sub>) δ ; 1.43 (15H, s), 1.57-1.69 (6H, m), 2.05-2.83 (5H, m), 2.88, 2.90 (3H, each, s), 3.22 (1H, m), 3.83 (2H, m), 4.12 (1H, m), 4.61 (1H, br-d, J = 13.0Hz), 4.90 (1H, s), 5.18 (1H, t, J = 8.4Hz), 6.24, 6.28 (1H, each s), 6.40-6.44 and 6.84-7.41 (8H, m)

(+) APCI MS m/z ; 652 (M<sup>+</sup> + 1)

#### Example 14

A suspension of N-[1-[(1-methanesulfonylspiro[indoline-3,4'-piperidine]-1'-yl) carbonyl]-2-(3,4'-dihydronaphthalen-2-yl) ethyl]-2-[(tert-butoxycarbonyl) amino]-2-methylpropanamide (181mg) in 4N hydrogen chloride in ethyl acetate (5ml) was stirred at ambient temperature for 5 hours and evaporated in vacuo. The residue was powdered from ethyl acetate and the powder was washed with diethyl ether to afford 2-amino-N-[1-[(1-methanesulfonylspiro[indoline-3,4'-piperidine]-1'-yl) carbonyl]-2-(3,4'-dihydronaphthalen-2-yl) ethyl]-2-methylpropanamide hydrochloride (139mg) as a solid.

mp ; 186.0-187.0 °C

IR (KBr) ; 2929, 1629, 1522, 1471, 1344, 1157 cm<sup>-1</sup>

<sup>1</sup>H NMR (MeOD-d<sub>3</sub>) δ ; 1.47-1.50 (3H, m), 1.58-1.61 (3H, m), 1.75-1.99 (4H, m), 2.29-2.41 (2H, m), 2.61-2.84 (5H, m), 2.96, 2.99 (3H, each s), 3.31 (1H, m), 3.92 (1H, m), 4.09 (1H, m), 4.54 (1H, bd-d J = 15.5Hz), 5.18 (1H, m), 6.33 (1H, d, J = 5.1Hz), 6.64-6.67 and 6.88-7.40 (8H, m)

(+) APCI MS  $m/z$  ; 551 ( $M^+ + 1$ )

#### Example 15

A mixture of N - [1 - [(1 - methanesulfonylspiro [indoline - 3, 4' - piperidine] - 1' - yl) carbonyl] - 2 - (3, 4 - dihydronaphtalen - 2 - yl) ethyl] - 2 - [(tert - butoxycarbonyl) amino] - 2 - methylpropanamide (540mg) and 10 % Pd/C (65mg) in methanol (10ml) was stirred in the presence of an atmospheric hydrogen at room temperature for 5 hours and filtered. The filtrate was evaporated in vacuo to afford N - [1 - [(1 - methanesulfonylspiro [indoline - 3, 4' - piperidine] - 1' - yl) carbonyl] - 2 - (1, 2, 3, 4 - tetrahydronaphthalen - 2 - yl) ethyl] - 2 - [(tert - butoxycarbonyl) amino - 2 - methylpropanamide (439mg) as a foam.

IR (film) ; 2927, 1714, 1637, 1506, 1485, 1454, 1350  $\text{cm}^{-1}$

$^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  ; 1.41 (9H, s), 1.45 (6H, s), 1.48 - 2.05 (8H, m), 2.45 - 2.79 (4H, m), 2.92 (3H, s), 3.02 - 3.26 (3H, m), 3.83, 3.85 (2H, each s), 4.07 - 4.18 (1H, m), 4.59 (1H, m), 4.92 (1H, s), 5.15 (1H, m), 7.00 - 7.42 (8H, m)

(+) APCI MS  $m/z$  ; 654 ( $M^+ + 1$ )

#### Example 16

A suspension of N - [1 - [(1 - methanesulfonylspiro [indoline - 3, 4' - piperidine] - 1' - yl) carbonyl] - 2 - (1, 2, 3, 4 - tetrahydronaphthalen - 2 - yl) ethyl] - 2 - [(tert - butoxycarbonyl) amino] - 2 - methylpropanamide (384mg) in 4N hydrogenchloride in ethyl acetate (5ml) was stirred at ambient temperature for 5 hours and evaporated in vacuo. The residue was powdered from ethyl acetate and the powder was washed with diethyl ether to afford 2 - amino - N - [1 - [(1 - methanesulfonylspiro [indoline - 3, 4' -

piperidine] - 1'-yl) carbonyl] - 2 - (1, 2, 3, 4-tetrahydronaphthalen - 2-yl) ethyl] - 2 - methylpropanamide hydrochloride as a solid.

mp ; 190.0 - 192.0 °C

IR (KBr) ; 2923, 1674, 1629, 1535, 1469, 1344, 1240  $\text{cm}^{-1}$

$^1\text{H}$  NMR ( $\text{MeOD} - \text{d}_3$ )  $\delta$  ; 1.60 (6H, m), 1.71 - 2.05 (8H, m), 2.52 - 2.91 (6H, m), 2.97 (3H, s), 3.43 (1H, m), 3.92 - 4.15 (3H, m), 4.50 (1H, m), 5.10 (1H, m), 6.88 - 7.38 (8H, m)

#### Example 17

N - [1 - [(1 - Methanesulfonylspiro [indoline - 3, 4' - piperidine] - 1'-yl) carbonyl] - 2 - (1, 2 - benzo - 1, 3 - cycloheptadien - 4 - yl) ethyl] - 2 - [(tert - butoxycarbonyl) amino - 2 - methylpropanamide] was prepared from 1' - [2 - amino - 3 - (1, 2 - benzo - 1, 3 - cycloheptadien - 4 - yl) propionyl] - 1 - methanesulfonylspiro [indoline - 3, 4' - piperidine] in a similar manner to Example 13.

FT IR (film) ; 1709, 1635, 1554, 1452, 1354, 1163  $\text{cm}^{-1}$

NMR ( $\text{CDCl}_3$ )  $\delta$  ; 1.44 (15H, s), 1.75 - 2.01 (6H, m), 2.04 - 2.77 (7H, m), 2.89, 2.91 (3H, each s), 3.17 - 3.24 (1H, m), 3.74 - 3.90 (2H, m), 4.06 - 4.14 (1H, m), 4.60 - 4.66 (1H, m), 4.90 (1H, s), 5.10 - 5.20 (1H, m), 6.32 (1H, d,  $J = 8.1$ ), 6.20 - 6.24, 6.78 - 6.85 and 7.00 - 7.41 (8H, m)

(+) APCI MS  $m/z$  ; 665 ( $\text{M}^+ + 1$ )

#### Example 18

N - [1 - [(1 - Methanesulfonylspiro [indoline - 3, 4' - piperidine] - 1'-yl) carbonyl] - 2 - (1, 2 - benzocyclohepten - 4 - yl) ethyl] - 2 - [(tert - butoxycarbonyl) amino - 2 - methylpropanamide] was prepared according to a similar manner to that of Example 15.

FT IR (film) ; 1711, 1641, 1512, 1458, 1452, 1350, 1248, 1161  $\text{cm}^{-1}$

$^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  ; 1.30 - 2.05 (26H, m), 2.69 - 2.75 (4H, m), 2.80



– 2.95 (5H, m), 3.80 – 3.83 (2H, m), 4.08 – 4.12 (1H, m), 4.50 – 4.55 (1H, m), 4.85 – 4.91 (1H, m), 5.05 – 5.11 (1H, m), 7.07 – 7.42 (8H, m)

(+) APCI MS  $m/z$  ; 667 ( $M^+ + 1$ )

#### Example 19

N – [1 – (1 – Methanesulfonylspiro [indoline – 3, 4' – piperidine] – 1' – yl) carbonyl] – 2 – (1, 2 – benzo – 1, 3 – cycloheptadien – 4 – yl) ethyl] – 2 – amino – 2 – methylpropanamide hydrochloride was prepared according to a similar manner to that of Example 14.

FT IR (KBr) ; 1631, 1529, 1479, 1469, 1346, 1159  $\text{cm}^{-1}$

(+) APCI MS  $m/z$  ; 565 ( $M^+ + 1$ )

$^1\text{H}$  NMR ( $\text{MeOD} - d_3$ )  $\delta$  ; 1.50, 1.51 (3H, each s), 1.60, 1.61 (3H, each s) 1.73 – 1.99 (6H, m), 2.37 – 2.82 (7H, m), 2.90, 2.94 (3H, each s), 3.30 – 3.40 (1H, m), 3.91, 3.93 (2H, each s), 4.10 – 4.15 (1H, m), 4.55 (1H, br – d,  $J = 14.2$ ), 5.15 – 5.20 (1H, m), 6.40 – 6.44 (1H, m), 6.82 – 6.89 and 7.07 – 7.39 (8H, m)

#### Example 20

N – [1 – (1 – Methanesulfonylspiro [indoline – 3, 4' – piperidine] – 1' – yl) carbonyl] – 2 – (1, 2 – benzocyclohepten – 4 – yl) ethyl] – 2 – amino – 2 – methylpropanamide hydrochloride was prepared according to a similar manner to that of Example 16.

FTIR (KBr) ; 1674, 1628, 1533, 1467, 1344, 1234, 1157  $\text{cm}^{-1}$

$^1\text{H}$  NMR ( $\text{MeOD}$ )  $\delta$  ; 1.49 – 1.73 (17H, m), 2.79 – 2.94 (6H, m), 2.97 (3H, s), 3.90 – 3.95 (3H, m), 4.44 – 4.48 (1H, m), 5.04 – 5.10 (1H, m), 7.06 – 7.40 (8H, m)

(+) APCI MS  $m/z$  ; 567 ( $M^+ + 1$ )

#### Example 21

1 - Ethyl - 3 - (3 - dimethylaminopropyl) carbodiimide hydrochloride (201mg) was added to a solution of 1' - [2 - amino - 2 - (2 - indanyl) acetyl] - 1 - methanesulfonylspiro [indoline - 3, 4' - piperidine] (300mg), N - tert - butoxycarbonyl -  $\alpha$  - methylalanine (160mg), and 1 - hydroxybenzotriazole (110mg) in dichloromethane (20ml) at ambient temperature, and the resulting mixture was stirred at the same temperature overnight.

The reaction mixture was partitioned between ethyl acetate and water. The organic layer was washed with water and brine, dried over magnesium sulfate, and evaporated in vacuo. The residue was chromatographed (n - hexane - ethyl acetate) over silica gel, and active fractions were concentrated in vacuo to give a foam.

A suspension of this material in 4N hydrogen chloride in ethyl acetate (5ml) was stirred at ambient temperature for 5 hours, and evaporated in vacuo. The residue was powdered from ethyl acetate and the powder was washed with diethyl ether to afford 2 - amino - N - [[1 - (2 - indanyl) - 2 - oxo - 2 - (1 - methanesulfonylspiro [indoline - 3, 4' - piperidine] - 1' - yl)] ethyl] - 2 - methylpropanamide hydrochloride (360mg) as a solid.

<sup>1</sup>H NMR (CD<sub>3</sub>OD)  $\delta$  ; 1.52 - 2.00 (10H, m), 2.76 - 3.20 (9H, m), 3.40 - 3.50 (1H, m), 3.90 - 4.15 (3H, m), 4.50 - 4.65 (1H, m), 4.90 - 5.01 (1H, m), 7.05 - 7.40 (8H, m)

(+) APCI MS m/z ; 525 (M<sup>+</sup> + 1)

#### Example 22

[N - (1R) - [1 - [(2 - Indanyl) methyl] - 2 - oxo - 2 - [4 - (2 - keto - 1 - benzoimidazoliny)] piperidin - 1 - yl] ethyl - 4 - piperidinecarboxamide hydrochloride was prepared from 1 - [(2R) - 2 - amino - 3 - (2 - indanyl) propionyl] - 4 - (2 - keto - 1 -

benzimidazoliny) piperidine in a similar manner to Example 21.

APCI MS  $m/z$  ; 516 ( $M^+ + 1$ )

#### Example 23

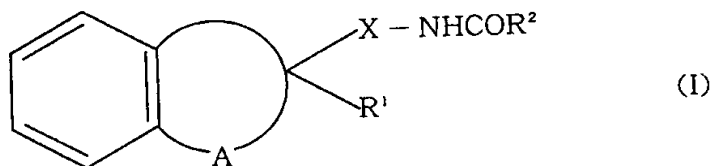
N - [1 - [(1 - Methanesulfonylspiro [indoline - 3, 4' - piperidine] - 1' - yl) carbonyl] - 2 - (1, 2 - benzocyclohepten - 5 - yl) ethyl] - 2 - [(tert - butoxycarbonyl) amino - 2 - methylpropanamide hydrochloride was prepared from 1 - [2 - amino - 3 - (1, 2 - benzocyclohepten - 5 - yl) propionyl] - 1 - methanesulfonylspiro [indoline - 3, 4' - piperidine] in a similar manner to Example 21.

$^1\text{H}$  NMR ( $\text{CD}_3\text{OD}$ )  $\delta$  ; 1.05 - 2.05 (17H, m), 2.70 - 2.87 (6H, m), 2.97 (3H, s), 3.90 - 4.05 (3H, m), 4.45 - 4.55 (1H, m), 4.99 - 5.06 (1H, m), 7.04 - 7.40 (8H, m)

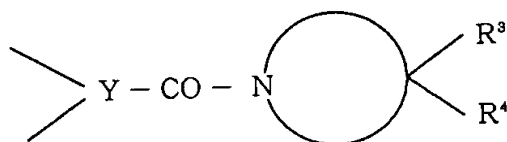
APCI MS  $m/z$  ; 567 ( $M^+ + 1$ )

## CLAIMS

1. A compound of the formula:



wherein R<sup>1</sup> is hydrogen and X is a group of the formula:

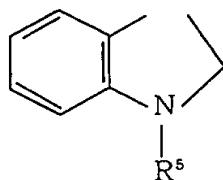


in which R<sup>3</sup> is esterified carboxy and R<sup>4</sup> is ar(lower) alkyl;

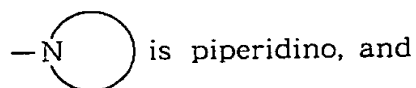
R<sup>3</sup> is cyano and R<sup>4</sup> is aryl;

R<sup>3</sup> is hydrogen and R<sup>4</sup> is 2-oxo-1-benzimidazoliny1; or

R<sup>3</sup> and R<sup>4</sup> are linked together to form

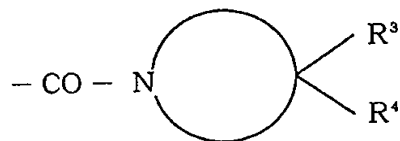



in which R<sup>5</sup> is acyl,



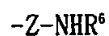
Y is lower alkanetriyl; or

R<sup>1</sup> is a group of the formula:



in which R<sup>3</sup>, R<sup>4</sup> and  are each as defined above and X is bond,

R<sup>2</sup> is 3-azetidiny, 4-piperidyl or a group of the formula:



in which R<sup>6</sup> is hydrogen or amino protective group, and

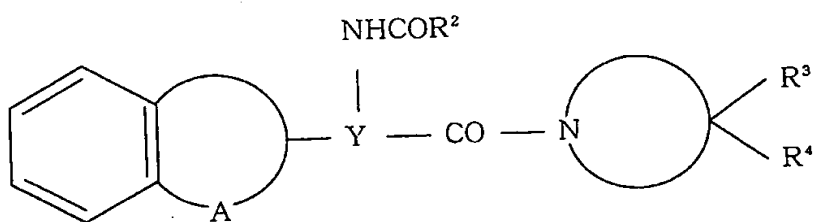
Z is lower alkylene or cyclo (lower) alkylene,

and

A is -(CH<sub>2</sub>)<sub>n</sub>-, in which n is 3, 4 or 5, or

$-\text{CH}=\text{CH}-(\text{CH}_2)_m-$ , in which  $m$  is 1, 2 or 3,  
and salts thereof.

2. A compound of the formula:



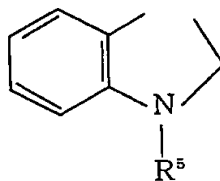
wherein  $R^2$ ,  $R^3$ ,  $R^4$ ,  $A$ ,  $Y$  and  $-\text{N}$  (circle) are each as defined in claim 1.

3. The compound of claim 2, wherein

$R^3$  is lower alkoxy carbonyl and  $R^4$  is benzyl;

$R^3$  is hydrogen and  $R^4$  is 2-oxo-1-benzimidazolyl; or

$R^3$  and  $R^4$  are linked together to form

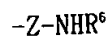


in which  $R^5$  is lower alkanesulfonyl,

$-\text{N}$  (circle) is piperidino,

$Y$  is lower alkanetriyl,

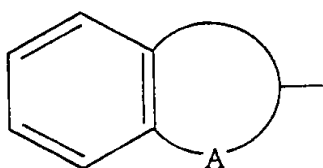
$R^2$  is 3-azetidyl, 4-piperidyl or a group of the formula:



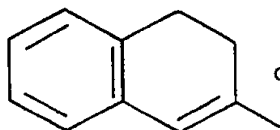
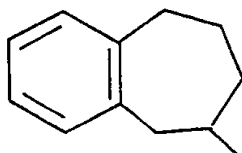
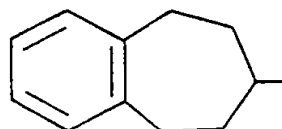
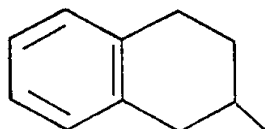
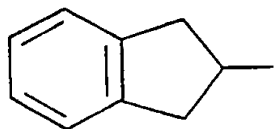
in which  $R^6$  is hydrogen or lower alkoxy carbonyl, and Z is lower alkylene  
or cyclo(lower) alkylene,

and A is  $-(CH_2)_n$  in which n is 3, 4 or 5, or  
 $-CH=CH-(CH_2)_m-$ , in which m is 1, 2 or 3.

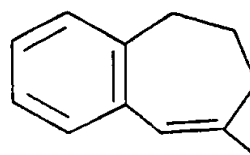
4. The compound of claim 3, wherein



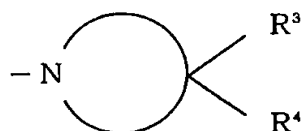
is the following formula :



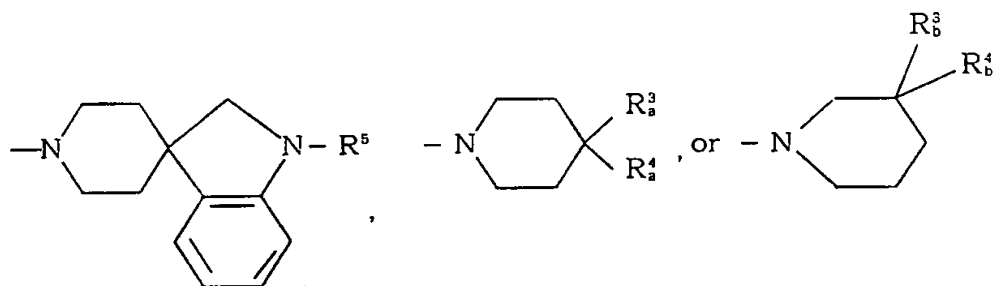
or



, and



is the following formula :



in which  $R^5$  is lower alkanesulfonyl,

$R_a^3$  is hydrogen,

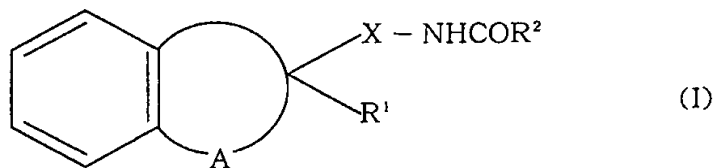
$R_a^4$  is 2-oxo-1-benzimidazoliny,

$R_b^3$  is lower alkoxy carbonyl and

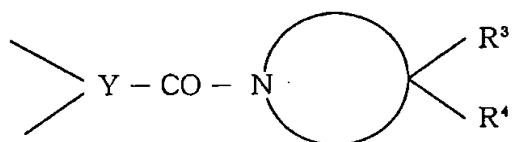
$R_b^4$  is benzyl.

5. A process for preparing a compound of the formula:





wherein  $R^1$  is hydrogen and  $X$  is a group of the formula:

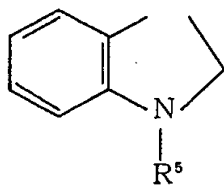


in which  $R^3$  is esterified carboxy and  $R^4$  is ar(lower) alkyl;


$R^3$  is cyano and  $R^4$  is aryl;

$R^3$  is hydrogen and  $R^4$  is 2-oxo-1-benzimidazolinyll; or

$R^3$  and  $R^4$  are linked together to form

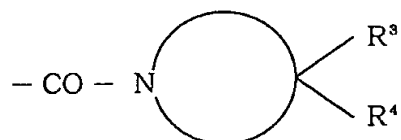


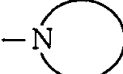
in which  $R^5$  is acyl,

—N  is piperidino, and

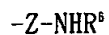
Y is lower alkanetriyl; or

R<sup>1</sup> is a group of the formula:



in which R<sup>3</sup>, R<sup>4</sup> and —N  are each as defined above and X is bond,

R<sup>2</sup> is 3-azetidiny, 4-piperidyl or a group of the formula:



in which R<sup>6</sup> is hydrogen or amino protective group, and

Z is lower alkylene or cyclo (lower) alkylene,

and

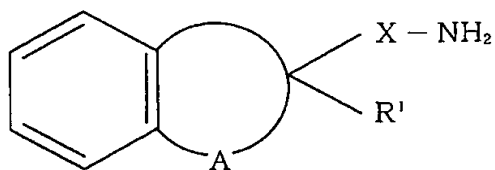
A is  $-(\text{CH}_2)_n-$ , in which n is 3, 4 or 5, or

$-\text{CH}=\text{CH}-(\text{CH}_2)_m-$ , in which m is 1, 2 or 3,

and salts thereof.

which comprises,

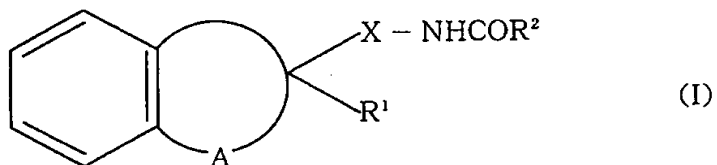
(1) reacting a compound of the formula:



wherein  $R^1$ ,  $X$  and  $A$  are each as defined above,  
 or its reactive derivatives at the amino group or a salt thereof,  
 with a compound of the formula:

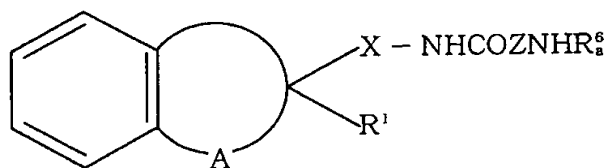


wherein  $R^2$  is as defined above,  
 or its reactive derivatives at the carboxy group or a salt thereof,  
 to give a compound of the formula:



wherein  $R^1$ ,  $R^2$ ,  $X$  and  $A$  are each as defined above,

(2)subjecting a compound of the formula:



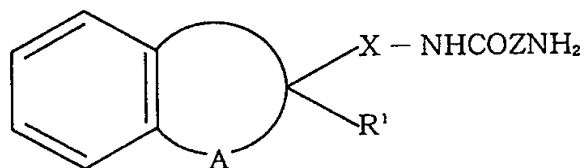
wherein  $R^1$ ,  $X$ ,  $A$  and  $Z$  are each as defined above,

$R_s^6$  is amino protective group,

or a salt thereof,

to removal of amino protective group,

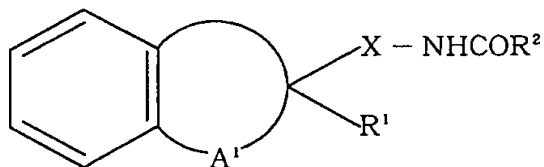
to give a compound of the formula:



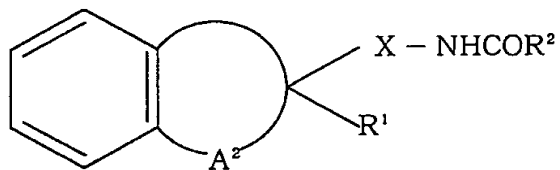
wherein  $R^1$ ,  $X$ ,  $A$  and  $Z$  are each as defined above,

or a salt thereof, or

(3)subjecting a compound of the formula:



wherein  $R^1$ ,  $R^2$  and  $X$  are each as defined above, and  
 $A^1$  is  $-\text{CH}=\text{CH}-(\text{CH}_2)_m-$ , in which  $m$  is 1, 2 or 3,  
 or a salt thereof,  
 to reduction reaction,  
 to give a compound of the formula:



wherein  $R^1$ ,  $R^2$  and  $X$  are each as defined above,  
 $A^2$  is  $-(\text{CH}_2)_n-$ , in which  $n$  is 3, 4 or 5.  
 or a salt thereof.

6. A pharmaceutical composition, which comprises, as an active ingredient, a compound of claim 1 or a pharmaceutically acceptable salt thereof in admixture with pharmaceutically acceptable carriers.

7. A use of a compound of claim 1 as a medicament which promotes

activity of growth hormone release for animals and human bodies.

# INTERNATIONAL SEARCH REPORT

International Application No

PCT/JP 98/01695

## A. CLASSIFICATION OF SUBJECT MATTER

IPC 6 C07D471/10 A61K31/445 C07K5/06

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 6 C07D A61K C07K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
E	WO 98 16527 A (TANIGUCHI KIYOSHI ; KURODA SATORU (JP); SHIMIZU YASUYO (JP); FUJISA) 23 April 1998 see claim 1	1-7
P, Y	WO 98 10653 A (PATCHETT ARTHUR A ; MERCK & CO INC (US); NARGUND RAVI (US); TATA JA) 19 March 1998 see claim 1	1-7
P, Y	WO 97 34604 A (MERCK & CO INC ; NARGUND RAVI (US)) 25 September 1997 see claim 1	1-7
Y	WO 97 11697 A (MERCK & CO INC ; YANG LIHU (US); MARQUIS ROBERT W (US); OLSON JOHN) 3 April 1997 see claim 1	1-7
	--- -/-	



Further documents are listed in the continuation of box C.



Patent family members are listed in annex.

### \* Special categories of cited documents :

- \*A\* document defining the general state of the art which is not considered to be of particular relevance
- \*E\* earlier document but published on or after the international filing date
- \*L\* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- \*O\* document referring to an oral disclosure, use, exhibition or other means
- \*P\* document published prior to the international filing date but later than the priority date claimed

- \*T\* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- \*X\* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- \*Y\* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- \*Z\* document member of the same patent family

Date of the actual completion of the international search

7 September 1998

Date of mailing of the international search report

23. 09. 98

Name and mailing address of the ISA

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Authorized officer

Gettins, M

# INTERNATIONAL SEARCH REPORT

Internati Application No  
PCT/JP 98/01695

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 96 05203 A (MERCK SHARP & DOHME ;LADDUWAHETTY TAMARA (GB); LEWIS RICHARD THOMA) 22 February 1996 see claim 1 ---	1-7
Y	WO 94 13696 A (MERCK & CO INC ;CHEN MENG HSIN (US); JOHNSTON DAVID B R (US); NARG) 23 June 1994 cited in the application see claim 1 ---	1-7
Y	GB 1 603 030 A (HOECHST AG) 18 November 1981 see claim 1 ---	1-7
Y	EP 0 615 977 A (MERCK & CO INC) 21 September 1994 see claim 1 -----	1-7



# INTERNATIONAL SEARCH REPORT

International application No.  
PCT/JP 98/01695

## Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:  
because they relate to subject matter not required to be searched by this Authority, namely:
2. ☒ Claims Nos.: 1-7  
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:  
see FURTHER INFORMATION sheet PCT/ISA/210
3. ☐ Claims Nos.:  
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

## Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

## FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Claims Nos.: 1-7

All the claims have only been searched partially. The current application describes a very broad and widely ranging range of chemical structures. All of the examples are similar to the compounds of the documents in the search report i.e. 4-spiroindoline piperidines and there is no specific indication that compounds other than these have actually been exemplified. It is impossible to classify all of the potential, but non-exemplified possibilities covered by the current application. The search has therefore been limited to spiroindoline derivatives i.e. the examples and the all claimed compounds containing moiety.

# INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/JP 98/01695

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Internal Application No

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International Application No

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